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Clinicopathologic Characteristics of Ovarian Carcinoma in Hasan Sadikin General Hospital Bandung

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ABSTRACT

Background
Ovarian carcinoma (OC) has several subtypes with overlapping histopathological presentation and usually has a poor prognosis. According to WHO, ovarian Mucinous Carcinoma (MC) is the most common subtype of OC in Southeast Asia, especially Indonesia, in contrast with a study in Taiwan which showed most cases from 2002-2015 was HGSC.

Objectives
This study aimed to report the incidence and clinicopathologic characteristics of OC between 2018-2023 tertiary Hospital in Bandung, Indonesia

Methods
We conducted a descriptive study, collecting OC data from medical records in Hasan Sadikin General Hospital, a tertiary referral hospital.

Results
The most common subtypes from 460 patients were MC (n=460;32%) based on histomorphology and immunohistochemistry, followed by Ovarian Endometrioid Carcinoma (EC) (n=460;21%). The mean age was 47.89 years old (range 14-81). We revealed EC's incidence was higher than ovarian High-Grade Serous Carcinoma (HGSC) (21% vs. 18%), discordant with the WHO report as the most common subtype. The largest OC reported was 70 cm in the greatest dimension found in MC, and the smallest OC was 3 cm found in Ovarian Clear Cell Carcinoma.

Conclusion
We found 460 cases of OC from 2018-2023, and the most common subtype of OC was ovarian MC. The overall mean age was 47.89 years old. The largest ovarian carcinoma was MC, 70 cm in the greatest dimension, and LGSC and CCC were the smallest. The most common surgical procedure was TAHBSO, and the average annual incidence was around 82 cases.

Keywords: Clinicopathologic, Indonesia, Ovarian Carcinoma

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INTRODUCTION

Ovarian carcinoma (OC) has several subtypes: high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), mucinous carcinoma (MC), clear cell carcinoma (CCC), and endometrioid carcinoma (EC), with different sometimes overlapping histopathological presentations and has poor overall prognosis. WHO reported OC as the eighth most common cancer diagnosis and cause of cancer death in women. [1] GLOBOCAN report in 2020 states the incidence of OC was 8.1:100.000. [2] Classification of OC relies on immunohistochemistry and molecular testing, although the tumor's morphology remains essential.[1]

The risk factors of OC are mainly related to genetic, hormonal, age, gynecologic, and lifestyle factors. Personal and family history of breast or ovarian carcinoma are associated with increased risk.[3] BRCA germline mutation has been associated with an increased risk of malignancy for breast and ovarian cancer, especially HGSC, but a study by Neff et al showed that only 22% of HGSC have BRCA1/2 mutation due to combination of germline and somatic mutation.[4] Some studies also consider endometriosis increases the risk of malignancy.[3,5] However, a gradual decline has observed in epithelial ovarian cancer with widespread use of oral contraceptive pills that have protective effects against OC after several years of use.[6]

The majority of cases of OC in the world are HGSC, a study by Teng et al, in Taiwan revealed that HGSC was slightly high proportion of OC from 2002 to 2015 than other subtypes, [7] but in certain parts of Southeast Asia, such as Indonesia and Singapore, MC was more common. A meta-analysis by Momenimovahed et al also showed higher proportion of non-mucinous ovarian cancer (97%) in which 70% were serous carcinoma and only 3% were MC.[3]

Mucinous carcinoma is an invasive mucinous neoplasm composed of gastrointestinal-type cells that gross appearance typically large, unilateral, solid, and cystic and has an overall prognosis of 91% for stage I. [1,8] High-grade serous carcinoma is a high-grade epithelial neoplasm with serous differentiation that is believed to arise from tubal-type epithelium, and gross appearance is usually bilateral, large, and exophytic and has an overall prognosis between 15%-45%. [1,9] Given the difference between the clinicopathologic and prognosis of each subtype and the limited available data on OC in Indonesia, we aim to report the clinicopathologic of OC in Indonesia.

METHODS

This is a retrospective study conducted in Dr. Hasan Sadikin General Hospital Bandung, Indonesia as an academic referral hospital. We have collected patients' medical record data who were diagnosed OC histologically between January 2018 and June 2023 in Hasan Sadikin General Hospital Bandung, Indonesia, or referred as OC to our hospital. We also recorded the age, tumor diameter, laterality, and stage according to the FIGO classification of each case. The exclusion criteria are carcinoma with unknown origin in the ovary, which was not yet examined immunohistochemically for the cell origin.

RESULTS

There were 460 OC cases between 2018-2023. The most common OC subtype was MC, followed by EC, CCC, HGSC, and LGSC (n=460; 32%, 21%, 19%, 18%, 9%). The age range of OC was 14-81 years old (mean 47.89). The youngest and the oldest cases we found were both diagnosed as MC. The average diameter of OC was 18.45 cm, with the largest being (Table 2) 70 cm found in MC and the smallest in LGSC and CCC. Most cases revealed unilaterality (76%) of the tumor rather than bilateral (15%). We found stage I and stage III OC were around the same. but we also found a lot of cases cannot determine the stage of OC.

We also found total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO) as the most common surgical procedure done for the patient (63%), followed by suboptimal debulking (6%), salpingo-oophorectomy (SO) (5%), fertility sparring (2%) and biopsy (2%). There are 109 cases (24%) in which surgery was not done in our facility.

Figure 1 shows the mean age of ovarian carcinoma by its subtype. The average age of HGSC we found is the oldest (52.5 years old) and the youngest in LGSC (42.41 years old). The incidence per year is explained in Figure 2. We saw around 82 cases per year, where 2021 was the lowest due to the COVID-19 pandemic. The highest case was in 2022, for 87 cases. The

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collected data until June 2023 showed 48 cases in half a year.

As seen in Figure 3, the gross appearance of OC was cystic with multilocular cysts (48%) and unilocular cysts (25%). We also reported 32 (7%) cases of tumor necrosis and 83 (18%) cases of papillary appearance. Ascites were found in 164 cases (36%), and of all the ascites found, there were 72 cases (44%) of malignant cells found in the ascites.

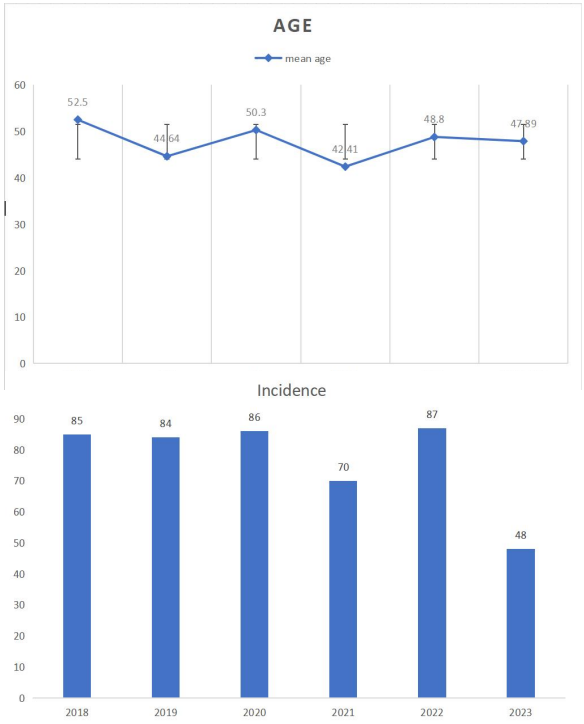


Figure 2. Graphic distribution of incidence per year.

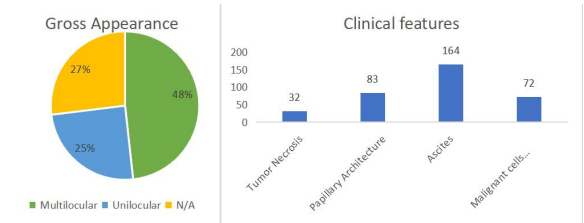


Figure 3. Gross Appearance and Clinical Features Diagram of Ovarian Carcinoma.

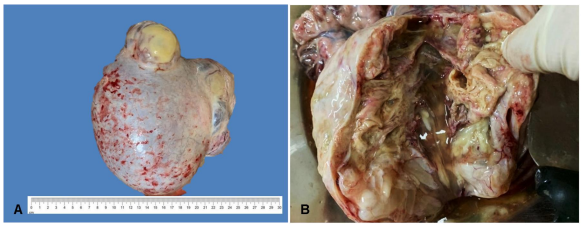


Figure 4. Gross appearance of Mucinous Ovarian Carcinoma. A. This picture showed an intact, smooth outer surface. B. solid and cystic component with mucinous content.

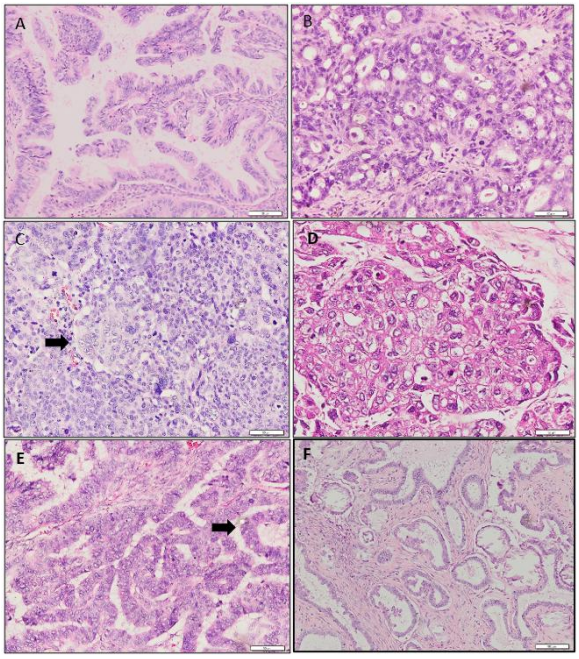


Figure 5. (A, B) Ovarian MC. A. 100 times magnification showed tumor cells composed of gastrointestinal-type cells. B. and 200 times magnification showed a cribriform pattern of MC. C. Ovarian EC under 200 times magnification showed a solid pattern of tumor cells, the black arrow showed squamous metaplasia of the tumor cells. D. Ovarian CCC 200times magnification displayed solid architecture composed of cells with eosinophilic and clear cytoplasm. E. The endometrioid-like pattern of HGSC under 200 times magnification, black arrow showed a gland-like structure resembling that of endometrioid carcinoma and increased size and marked atypical nuclei. F. LGSC displayed papillary architecture layered by tumor cells with moderate atypia.

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Table 1. Characteristics of Ovarian Carcinoma based on clinicopathologic.

Ovarian Carcinoma Characteristics		Mean (SD)
OC Subtypes (N=460;100%)		
MC	148 (32%)	
EC	98 (21%)	
CCC	89 (19%)	
HGSC	84 (18%)	
LGSC	41 (9%)	
Age	14-81 years old	
<45 years old	169 (37%)	47.89 ± 11.77
≥45 years old	291 (63%)	
Tumor diameter	3-70 cm	18.45 ± 8.62
Laterality		
Unilateral	353 (76%)	
Bilateral	68 (15%)	
Cannot determine	39 (8%)	
OC clinical stage		
I	124 (27%)	
II	81 (18%)	
III	124 (27%)	
IV	24 (5%)	
Cannot determined	107 (23%)	
Surgical procedure		
TAHBSO	288 (63%)	
Suboptimal debulking	26 (6%)	
SO	21 (5%)	
Fertility sparring	9 (2%)	
Biopsy	7 (2%)	
N/A	109 (24%)	

MC=Mucinous carcinoma, SO=Salpingo-oophorectomy, EC=Endometrioid Carcinoma, N/A=Not available, CCC=Clear cell Carcinoma, HGSC=High-grade Serous Carcinoma, LGSC=Low-grade Serous Carcinoma, SD=Standard Deviation, TAHBSO=Total Abdominal Hysterectomy and Bilateral Salpingo-oophorectomy.

Table 2. Clinicopathologic characteristics of ovarian carcinoma subtypes.

	MC (n=148)	EC (n=98)	CCC (n=89)	HGSC (n=84)	LGSC (n=41)
Mean age (SD)	44.64 ± 13.10	50.3 ± 11.01	48.8 ± 7.67	52.5 ± 9.620	42.41 ± 14.51
<45 years old	77 (52%)	31 (32%)	22 (25%)	15 (18%)	24 (59%)
≥45 years old	71 (48%)	67 (68%)	67 (75%)	69 (82%)	17 (41%)
Tumor diameter					
Mean (SD)	23.3 ± 8.61 cm	16.57 ± 8.61 cm	15.72 ± 8.63 cm	17.18 ± 8.51 cm	13.85 ± 8.64 cm
Range (cm)	6-70 cm	4.5-50 cm	3-40 cm	3.2-41 cm	3-30 cm
Laterality					
Unilateral	132 (89%)	79 (81%)	68 (76%)	48 (57%)	27 (66%)
Bilateral	9 (6%)	11 (11%)	13 (15%)	26 (31%)	9 (22%)
Cannot determine	8 (5%)	8 (8%)	8 (9%)	10 (12%)	5 (12%)
Clinical Stage					
I	60 (41%)	27 (28%)	17 (19%)	9 (11%)	9 (22%)
II	19 (13%)	15 (15%)	17 (19%)	19 (23%)	11 (27%)
III	25 (17%)	32 (33%)	25 (28%)	32 (38%)	10 (24%)
IV	5 (3%)	6 (6%)	4 (4%)	9 (11%)	0 (0%)
Cannot determine	39 (26%)	18 (18%)	26 (29%)	15 (18%)	11 (27%)

MC=Mucinous carcinoma; EC=Endometrioid Carcinoma; CCC=Clear cell Carcinoma; HGSC=High-grade Serous Carcinoma; LGSC=Low-grade Serous Carcinoma; SD=Standard Deviation

DISCUSSION

Ovarian carcinoma is a primary malignant epithelial tumor arising in the ovary. OC has several subtypes, which are classified by histomorphology. There are differences in most cases we found in Indonesia that show MC in contrast to traditionally that the most common is HGSC. In the present study, from 460 cases of OC, the incidence of HGSC is ranked 4th among overall cases. In one study by Sung et al., the reason for this difference is still not apparent but presumed to be linked with geographical and ethnic differences and still needs further investigation.[1,10] The only possible

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risk factor correlated with MC to date is tobacco smoking,[11] but still does not explain geographical and ethnic differences.

Ovarian carcinoma usually presents in much later years, as age strongly correlates with ovarian cancer risk.[11,12] In our study, the mean age of OC cases was 47.89 years, and 63% cases were diagnosed ≥ 45 years. We observed the mean age is a few years younger than the WHO report and a study by Sindani et al. that revealed the mean age was 55 years old.[1.13] The reason for this might correlate with the number of MC cases we found in our study, which outnumbers HGSC.

All the surgical procedures followed NCCN guidelines for epithelial ovarian cancer. Some of the cases after comprehensive surgical staging were decided to undergo fertility sparring surgery, which performed unilateral SO or bilateral SO with uterine preservation.These cases were performed for patients with young age, early-stage disease, and fertility still desired. In cases of inoperable OC, surgical staging with biopsy was performed to determine the subtype of OC.[14]

The measurement of OC usually appeared as a large mass.[1] In this study, we found the mean diameter of OC was 18.45 cm, and we found an enormous OC case with a 70 cm size diagnosed as MC. This finding is concordant with all the previous studies.[1,11,15] The smallest case we found was LGSC and CCC (Table 2).

Ovarian carcinoma can occur on one side or both ovaries. Several OC subtypes are prone to occur bilaterally, such as HGSC and LGSC.[1,12] There are some cases of OC where the clinician could not determine the tumor's original location. This may be the consequence of oversized tumors or the tumor had already ruptured by the time of surgery.

The clinical staging of OC recognized was the FIGO classification, which we also use in this study. We found stage I and stage III as the most common stages of OC. Then we discovered quite a lot of cases could not be appropriately staged due to many cases being referred only to undergo chemotherapy or immunohistochemistry tests.

A study from Kurnit and Frumovitz explained that MC has low metastatic potential and is usually limited to the ovary in 95% of cases and <5% of cases with stage I have recurrence.[8] Tumor size and laterality may also help differentiate MC from metastatic disease, mainly from the gastrointestinal tract.[11,15] If the tumor is unilateral and > 10cm in diameter, in about 80% of cases, the ovary was the tumor's primary site,[15] as reflected in our study (Table 2), that unilateral MC was 89% of the case. On the other hand, a study by Koshiyama et al. informed that mucinous carcinoma, mainly the intestinal type, may evolve from transitional cells or metaplasia at the fallopian tube-peritoneal junction,[16] due to a different pathway histogenesis of MC from another OC. At the first event, KRAS mutation develops, and HER2 amplification or TP53 mutation occurs later during malignant transformation.[11]

Even though LGSC is associated with more indolent clinical courses than HGSC[17,18], our study found 24% (n=41) cases of all LGSC in stage III. The higher stage of LGSC will increase the risk of recurrence.[18] Based on a study by Grisham et al., there is a difference between resection in HGSC and LGSC in which optimal cytoreduction remains critical in LGSC even if complete gross resection is unattainable.[17]

Ovarian CCC is a high-grade carcinoma with characteristics of histologic and immunophenotypic features and, in association with endometriosis,[19] should often present at an early stage.[20] In contrast, we discovered that the most we found in CCC was stage III. This might be related to the small sample size and indolent nature of CCC so that at an early stage, the patient is asymptomatic. However, a study by Tang et al. revealed no statistically significant difference among the chemotherapy cycles for stages I to IV, and 23,6% of patients were refractory or resistant to chemotherapy.[20]

Ovarian EC is a distinct subtype of epithelial ovarian cancer associated with endometriosis and Lynch syndrome.[21] A study by Zhou et al. discovered that from 211 patients with EC, 54% of cases were found in stage I and 25.6% in stage III.[22] This is slightly different in this study, in which stage III is more common than stage I (33% and 28%, respectively).

The clinical features of OC, as seen in Figure 3. show the OC's most common gross appearance was a multilocular cyst, most of which was MC subtype; as reported by WHO, the multilocular cyst was a common finding in MC. The unilocular cysts we found were more common in the CCC subtype. The WHO reports that CCC is typically unilateral, and the cut

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surface varies from solid to cystic.[1] In some studies, ascites correlate with the advanced stage of OC.[23] We found in our study that 36% of OC have ascites, and 44% of all ascites have malignant tumor cells found inside, which is relatively lower compared to a study by Ayhan et al. that found 46.3% advanced stage OC had ascites.[24] We also found a higher proportion of HGSC had ascites 59,5% than any other subtypes.

Tumor necrosis was found in 32 patients, as seen in Figure 3. Even though we did not record whether the patient was given neoadjuvant chemotherapy at the time of surgery or not, but a study by Le et al explains that lack of tumor necrosis or minimal tumor necrosis after a neoadjuvant therapy was an independent risk factor for recurrent disease.[25]

We found papillary architecture in 83 patients in all of OC subtypes, usually papillary architecture is associated with serous borderline tumor in several study.[26,27] However, in our study we did not find any significant difference between all of OC subtypes for papillary architecture. On side note, a study by Sangoi et al explains that papillary architecture in CCC can mimic Serous Borderline Tumor of ovary,[26] in this case, we need to perform immunohistochemistry panel for differentiating between those tumors.

CONCLUSION

We found 460 cases of OC from 2018-2023, and the most common subtype of OC was ovarian MC. The overall mean age was 47.89 years old. The largest ovarian carcinoma was MC, 70 cm in the greatest dimension, and LGSC and CCC were the smallest. The most common surgical procedure was TAHBSO, and the average annual incidence was around 82 cases.

Acknowledgments

The authors declare that they have no financial conflict of interest regarding the content of this report.

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