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The Characteristics of Sociodemography, Histopathologic Features, Stage, and Management of Ovarian Cancer in Dr. Ramelan Navy Hospital Surabaya

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ABSTRACT

Background: Ovarian cancer is considered a silent killer disease, mainly due to the late diagnosis. It is often diagnosed at an advanced stage, thus increasing the mortality rate. Ovarian cancer can happen to any age, with different characteristics according to the age group, the most often being the epithelial type.

Methods: This research is a descriptive study with a quantitative method. This study aims to determine the characteristics and histopathological features of ovarian cancer in Dr. Ramelan Navy Hospital from January 2019 to December 2021. There were 155 samples out of 635 patients, with the information acquired through medical records.

Results: The highest incidence of ovarian cancer occurs in the 40-60-year-old group at 52.9%. Among all participants, 85.8% of patients were not employed. Of most histopathological features in epithelial ovarian cancer, 34.8% were the serous carcinoma subtype. The majority of these cases were diagnosed at stage IIIC at 21.3%, and the most prevalent treatment for ovarian cancer was surgery and chemotherapy at 49.7%.

Conclusions: The most common type of ovarian cancer is epithelial ovarian cancer, a subtype of serous carcinoma, with histopathological features of round nucleated anaptic cells, prominent nucleoli, forming acini, papillae, and thin connective tissue stroma.

INTRODUCTION

The most common malignancy of the female reproductive system is ovarian cancer. The World Health Organization (WHO) reported that in 2020, ovarian cancer ranked ninth as the most common cancer in women in the world. Ovarian cancer has the highest mortality rate compared to other gynecological malignancies such as cervical cancer, uterine cancer, vaginal cancer, and vulvar cancer [1]. The incidence of ovarian cancer is increasing from year to year and occurs almost all over the world. Global Burden Cancer (Globocan) 2020 reported that the incidence of ovarian cancer reached 313,959 with a mortality rate of 207,252 in the world [2]. The high mortality rate is because the initial stage of the disease is asymptomatic until the advanced stage, so patients are usually only diagnosed at the final stage or called the silent killer [3].

Ovarian cancer in Indonesia is the third most common cancer in women with 4.1% of deaths after breast cancer and cervical cancer. The prevalence of ovarian cancer is lower than breast cancer, but the mortality rate is three times higher and deaths from this cancer are expected to increase significantly by 2040. Cancer growth with late recognition of symptoms and inappropriate screening results in cancer being diagnosed at an advanced stage, increasing the mortality of ovarian cancer patients [4].

Ovarian cancer is a mass growth of abnormal tissue in the ovary and is often undetectable unless it metastasizes in the abdomen and pelvis [5]. Only about 20% of ovarian cancers are diagnosed at the first stage

despite 90% of patients responding well to therapy at stage I. Metastatic disease is divided into 3 categories: Stage II of ovarian cancer metastasizes to the pelvic area, and stage III happens after the disease spreads to the abdomen or outside the peritoneal area. At Stage IV, the recovery rate begins to decrease substantially [6].

The clinical manifestations of ovarian cancer are usually asymptomatic and nonspecific, but signs and symptoms that may raise suspicion are the presence of an adnexal mass in the abdomen. The patient usually comes with bloating complaints due to the accumulation of ascitic fluid in the abdomen. Other complaints include increased frequency of urination, lower abdominal pain, edema periphery, and shortness of breath [7,8]. Malignant-associated effusion occurs at a more advanced stage, which allows the spread of tumor cells to the peritoneum and the formation of metastases [9].

Ovarian cancer can be divided into two subtypes based on cell/site of origin, pathological grade, risk factors, prognosis, and treatment, namely epithelial ovarian cancer and non-epithelial ovarian cancer. Epithelial ovarian cancer is most common in all racial/ethnic groups, accounting for 90% of all cases. Classification of ovarian cancer based on tumor cell histology includes serous (52%), endometrioid (10%), mucinous (6%), and clear cell (6%), with a quarter being rarer or unspecified subtypes. Non-epithelial ovarian cancers are usually less aggressive than epithelial malignancies. Germ cell and sex cord-stroma tumors make up the majority of non-epithelial cancers, accounting for only 3% and 2%, respectively, of all ovarian cancers. Epithelial ovarian cancer of the serous carcinoma subtype has the most frequent incidence rate [10].

Epithelial ovarian cancer is usually diagnosed at an advanced stage, as the disease has no obvious symptoms in the early stages. Abdominal swelling caused by ascites is the most common sign of advanced stages. Research suggests that persistent nonspecific symptoms in the months before diagnosis occur in some women, including back pain, pelvic or abdominal pain, abdominal distension, difficulty eating or feeling full quickly, indigestion, vomiting, changes in bowel habits, and urgency or frequency of urination. Some non-epithelial ovarian cancer patients often present with more specific early signs, including irregular vaginal bleeding [10].

Based on the data above regarding the high number of ovarian cancer cases, especially serous type epithelial ovarian cancer the high mortality rate of women due to ovarian cancer, and the tendency to increase the incidence of ovarian cancer each year. Research on the problem of ovarian cancer in Dr. Ramelan Navy Hospital has never been done. The purpose of this study was to determine the sociodemographic characteristics, histopathological features, staging, and management of ovarian cancer at Dr. Ramelan Navy Hospital from 2019 until 2021.

METHODS

This research is a descriptive study with quantitative methods using secondary data sources, which are patients' medical records. The population of this study was medical records of female patients who had ovarian cancer at Dr. Ramelan Navy Hospital for the period January 2019 until December 2021. The sampling technique used was the total sampling technique by taking all selected samples according to the criteria set by the researcher.

The inclusion criteria in this study included the medical records of female patients who had a diagnosis of ovarian cancer, the medical records of ovarian cancer patients at Dr. Ramelan Navy Hospital for the period January 2019 until December 2021 as well as medical records of ovarian cancer patients with variable data on age, occupation, histopathological features, stage of ovarian cancer and ovarian cancer therapy. Exclusion criteria in this study were incomplete, lost, and damaged medical record data.

Data collection and retrieval procedures were carried out after obtaining ethical approval from the ethics committee of Dr. Ramelan Navy Hospital. The research was carried out from May 2022 to December 2022, starting with looking for references and bibliographical sources then compiling proposals and arranging research permits, after obtaining research permits, researchers can access and collect medical record data according to the variable table that has been made and continues the processing process data.

RESULTS

Research data in this study included patient sociodemography, histopathological classification of ovarian cancer, cancer stage, and ovarian cancer management. The total amount of data on ovarian cancer patients over 3 years was 635 patients, and 155 medical records of ovarian cancer patients met the inclusion criteria.

Sociodemographic characteristics observed in this study include age and occupation. The distribution of the proportion of ovarian cancer samples based on age and occupation can be seen in **Table 1**. The largest number of samples were in the 40–60 year age group, namely 82 patients (52.9%). Most of the samples did not work as many as 103 patients (66.5%).

Based on the origin of tumor cells/histopathological classification, patients with ovarian cancer are presented in **Table 2**. Among 155 patients, 134 patients were diagnosed with epithelial ovarian cancer (86.5%) and 21 patients had non-epithelial ovarian cancer (13.5%). Among the types of ovarian cancer found, 54 patients (34.8%) were diagnosed with serous carcinoma, 46 patients (29.6%) had mucinous carcinoma, 13 (8.4%) patients had endometrioid carcinoma, 17 patients (11%) had clear-cell carcinoma, and 4 patients (2.6%) had

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Table 1. Distribution of patients based on sociodemographic characteristics

Sociodemography	Frequency (n)	Percentage (%)
Age		
<40 years	31	20.0
40–60 years	82	52.9
>60 years	42	27.1
Occupation		
Working	52	33.5
Non-working	103	66.5

Table 2. Distribution of patients based on cell origin/ histopathology

Histopathological Classification	Frequency (n = 155)	Percentage (%)
Epithelial		
Serous carcinoma	54	34.8
Mucinous carcinoma	46	29.6
Endometrioid carcinoma	13	8.4
Clear-cell carcinomas	17	11
Seromucinous	4	2.6
Non-epithelial		
Ovarian germ cell tumors (OGCT)		
Disgerminoma	2	1.3
Immatur Teratoma	8	5.2
Yolk Sac Tumors	1	0.6
Ovarian sex cord-stromal tumors		
Tumor cell Granulosa	10	6.5
Tumor cell Sertoli Leydig	0	0
Gynandroblastoma.	0	0

Table 3. Sample distribution based on cancer stage

Ovarian Cancer Stage	Frequency (n = 155)	Percentage (%)
Stage I		
IA	8	5.2
IB	6	3.9
IC	10	6.5
Stage II		
IIA	28	18.1
IIB	29	18.7
Stage III		
IIIA	15	9.7
IIIB	17	11.0
IIIC	33	21.3
Stage IV		
IVA	9	5.8
IVB	0	0

Table 4. Sample distribution based on management

Intervention for Ovarian Cancer Patients	Frequency (n = 155)	Percentage (%)
Surgery	52	33.5
Surgery + Chemotherapy	77	49.7
Chemotherapy	26	16.8
Radiotherapy	0	0

seromucinous carcinoma. For patients with non-epithelial ovarium cancer in Ovarian Germ Cell Tumors (OGCT), 2 patients (1.3%) had dysgerminoma, 8 patients (5.2%) had immature teratoma, 1 patient (0.6%) had Yolk Sac Tumors. In Ovarian sex cord-stromal tumors, 10 patients (6.5%) had granulosa cell tumors, and no patients with Sertoli Leydig cell type ovarian cancer and Gynandroblastoma were found.

Based on the cancer stage distribution in **Table 3**, it can be seen that the highest number of cases were in the stage IIIC group of 33 people (21.3%), then stages IIB, IIA, IIIB, IIIA, IC, IVA, IA, IB with 29 people (18.7%), 28 people (18.1%), 17 people (11.0%), 15 people (9.7%), 10 people (6.5%), 9 people (5.8%), 8 people (5.2%), 6 people (3.9%) respectively, and no patients were found in the stage IVB group.

Table 4 presents the distribution based on therapy/ management. In the data of 155 patients, 52 patients (33.5%) underwent surgery, 77 patients (49.7%) underwent surgery + chemotherapy, 26 patients (16.8%) underwent chemotherapy and there were no ovarian cancer patients undergoing radiotherapy. Our result displayed that chemotherapy treatment that combines carboplatin and paclitaxel series 6 drugs was more widely used in 98 patients.

DISCUSSION

The age distribution of ovarian cancer patients obtained in **Table 1** shows that the highest age frequency of ovarian cancer patients is in the 40–60-year age group, which is 82 subjects (52.9%) with an average age of 51 years. The findings in this study are in line with Froyman et al. [11] study which reported that ovarian cancer is most often found in the age group of 42–66 years. In the European Prospective Investigation

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into Cancer and Nutrition (EPIC) cohort study, age at menopause (>52 years) was associated with an increased risk of ovarian cancer [12].

The chance of getting ovarian cancer goes up with age. This is because ovarian cancer usually presents at the age of menopause (over 55 years). In this study ,it was found that the age group that had the highest percentage was the age group of 40-60 years. A study by Reid et al. [12] also highlights the relationship between early menarche and late menopause, resulting in longer exposure to estrogen thus increasing the number of ovulation cycles. The rise in estrogen levels can cause proliferation and increase the possibility of DNA damage and mutation. This condition allows ovarian cancer to occur.

According to the Gonadotropin theory, ovarian activity is controlled by gonadotropins. At menopause, increased gonadotropins will cause increased ovarian malignancy. The gonadotropin theory's hypothesis states that ovarian cancer develops as a consequence of the overstimulation of ovarian tissue by pituitary gonadotropins (Lutheinizing Hormone or Follicle Stimulating Hormone). The effect of gonadotropins can be exerted either directly through activation of gonadotropin-responsive genes in cells undergoing malignant transformation or indirectly through stimulation of ovarian sex steroid production which can affect malignant transformation through paracrine or endocrine mechanisms [13].

The highest proportion of ovarian cancer patients who were treated based on work were patients who did not work as many as 103 people (66.5%) compared to patients who worked as many as 52 people (33.5%). This is in line with the results of a study conducted at Cipto Mangunkusumo Hospital, Jakarta in 2018, which found that 78.8% of ovarian cancer patients were housewives or classified as unemployed [14].

A research result shows that there is a greater risk of experiencing epithelial-type ovarian cancer in women in teaching occupations [15]. This indicates that working women who are familiar with reading and keeping up with current information are still at risk of developing ovarian cancer, even though they may have more access to health literature through their line of work.

The results of data collection for histopathological classification of patients with ovarian cancer are presented in **Table 2**. There were 134 patients with epithelial ovarian cancer (86.5%) and 21 patients with non-epithelial ovarian cancer (13.5%). The type of epithelial ovarian cancer found consisted of serous carcinoma in 54 patients (34.8%). The findings in this study are in line with the research of Xiong et al. (16) which found that ovarian cancer of the serous carcinoma subtype was found more frequently in 160 patients (68%) from a total of 232 ovarian cancer patients. **Figure 1A** presents the histopathological features of serous carcinoma found the formation of round nucleated anaplastic cells, prominent nucleoli, forming acini and

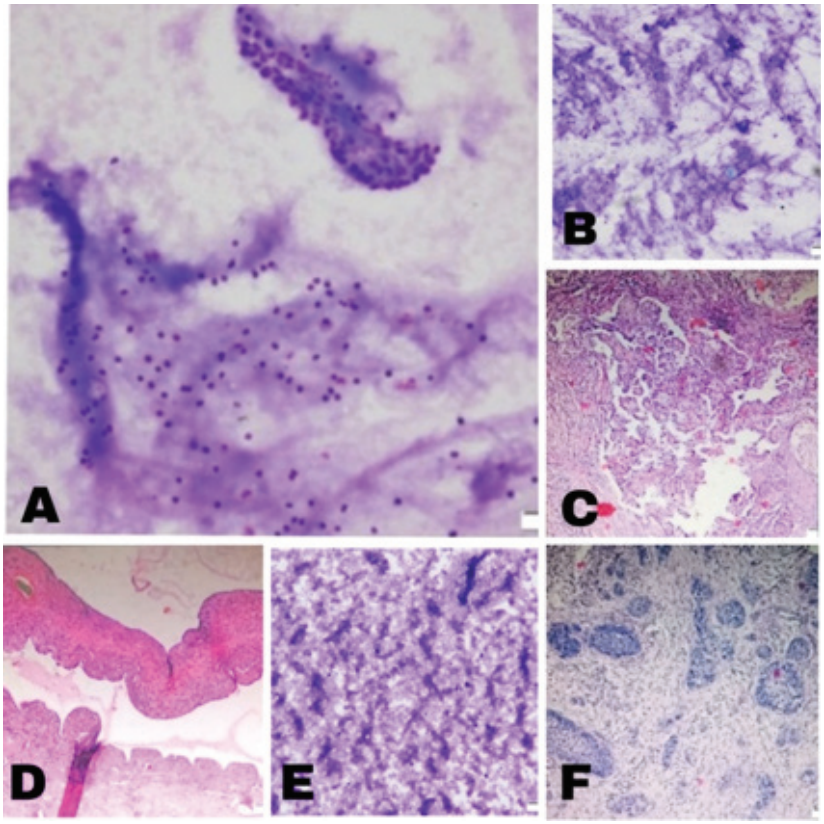

Figure 1. Histopathological of ovarian cancer.
(A) Epithelial serous type;
(B) Epithelial mucinous type;
(C) Epithelial clear cell type;
(D) Epithelial endometroid carcinoma type;
(E) Non-epithelial granulosa cell type;
(F) Non-epithelial immature teratoma type.

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papillae, and thin connective tissue stroma. There was also a mass of necrosis with mononuclear (MN) and polymorphonuclear neutrophilic (PMN) inflammatory cells.

The second most common histopathological classification after serous carcinoma is mucinous carcinoma, followed by clear-cell carcinomas and endometrioids. This study was also in accordance with Hlaváč et al. [17] which stated that serous subtype histopathology was more commonly found, occurred in 39 patients (80%), followed by mucinous in 5 patients (10%), Clear-cell in 3 patients (6%) and Endometrioid in 2 patients (2%). The histopathological features of mucinous carcinoma are ovarian tissue in the form of multilocular cysts, with the growth of anaptic cells with round nuclei, pleomorphic, coarse chromatin, lined with columnar epithelium containing mucin, part of the epithelium is atypical and forms acini and papillae, accompanied by a mass of extensive necrosis are presented in **Figure 1B**.

The histopathological appearance of clear-cell carcinomas in **Figure 1C** has the form of proliferation of oval nucleated anaplation cells, pleomorphic, prominent nucleoli, and eosinophilic bright cytoplasm, arranged in a solid structure and papillary with hobnail formation. Endometrioids have a histopathological picture of anaplastic cell growth, pleomorphic nuclei, vesicular, forming acini and papillae, fibromuscular stroma with infiltration into the stroma, connective tissue, and necrotic masses are presented in **Figure 1D**. While the Seromucinosa subtype is described as cyst-shaped ovarian tissue with cyst walls lined with simple cuboidal epithelial cells located at the base, extensive cytoplasm with periapical mucin, and few MN inflammatory cells seen infiltrating the stroma.

The results of non-epithelial ovarian cancer research found in the medical records of Dr. Ramelan Navy Hospital showed the same results in Bossart et al. [18] study. The highest percentage was found in Granulosa cell tumors with 61% in 92 patients. Granulosa cell tumor histopathology in **Figure 1E** shows tumor growth containing the proliferation of oval nucleated cells, salt and paper chromatin with nuclear groove appearance, arranged nodularly bounded by connective tissue septa, plexner formations, wintersteiner rosettes, and call exner bodies are also visible.

In contrast to Goyal et al. [19] study, it was found that the percentage of dysgerminoma (80%) cases were higher than those with immature teratomas (53%). Histopathological picture Dysgerminoma shows lobulated tissue with anaplastic cell growth, rounded vesicular nuclei, prominent nucleoli, uniform, extensive clear cytoplasm, some clustered, some forming pseudoglandular, some solid lymphocytes, macrophages with bleeding and necrosis. The immature teratomas obtained from medical records were ovarian tissue in the form of cysts, consisting of cartilage, fatty tissue and muscle tissue, dilated blood vessels, and MN inflammatory cells were also seen in **Figure 1F**.

The most common type of surface epithelial ovarian cancer is thought to be related to the process of metaplasia due to repeated trauma and exposure to cytokines and reactive oxygen species during ovulation. Other types occur presumably because ovarian surface epithelial cells experience invagination into the stroma forming cortical inclusion cysts which are exposed to various hormones such as luteinizing hormone and follicle-stimulating hormone. This process triggers the development of cell metaplasia into a more complex epithelium imitating Mullerian-derived organs [20].

Differentiation of specialized ovarian surface epithelial cells i.e. a Mullerian type of epithelium similar to that of the fallopian tube, endometrium, or endocervix, allows selective growth through changes in hormone factor/growth receptors and their susceptibility. Indeed, the most common type of ovarian tumor is serous adenocarcinoma which resembles the fallopian tube epithelium, while endometrioid tumors resemble endometrial and mucinous epithelial tumors originating from the endocervix [13].

Of 155 patients diagnosed with ovarian cancer, 33 people were diagnosed with stage IIIC (21.3%). This study is in line with Huang et al. [21] study which stated that 90 patients (64.3%) were diagnosed with ovarian cancer at stage III. Based on the data collected, it can be concluded that the results are in accordance with the theory. Ovarian cancer has no clear symptoms, so there is often a delay in diagnosis, and ovarian cancer is found at an advanced stage [4].

Ovarian cancer of the serous and endometrioid subtypes is more often diagnosed at a late stage (III and IV) which states that the serous and endometrioid subtypes have a high grade so that they are more malignant and develop more quickly. Mucinous and clear cell subtypes are one of the subtypes of type I ovarian surface epithelial cancer which has a slower and more benign course. The histopathological type of stromal sex cord has a high recurrence rate, especially in cases with a tumor diameter of ≥7 cm [20].

Surgical medical management of ovarian cancer patients at Dr. Ramelan Navy Hospital is divided into surgical staging and debulking. Surgical staging is divided into conservative surgical staging and complete surgical staging. Conservative surgical staging is carried out in patients who still need reproductive function with certain indications. Unilateral salpingo-oophorectomy wishing to preserve the contralateral uterus and ovary (fertility-preserving surgery) may be considered for patients with overt disease in the early stages [22].

Complete surgical staging is performed on early-stage ovarian cancer. The best management for stage I and

II lesions is total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) with accurate surgical staging. At many institutions, omentectomy is part of the surgical staging of stage I lesions [22]. Surgical management of stage III-IV ovarian cancer is carried out on the principle of debulking. Debulking is divided into optimal debulking and suboptimal debulking. Optimal debulking is done if there is no residual tumor mass (complete resection) or if the tumor mass is < 1cm (incomplete resection). Suboptimal debulking is performed when the remaining tumor mass is ≥ 1 cm.

All patients with stage II should be given adjuvant chemotherapy. The optimal number of cycles in patients with stage I has not been definitively established, but usually between 3 and 6 cycles is given. Patients who have undergone primary cytoreduction (debulking) should have chemotherapy added after surgery. The accepted standard is 6 cycles (series 6) of platinum-based combination chemotherapy, with platinum (carboplatin or cisplatin) and a taxane (paclitaxel or docetaxel).

CONCLUSIONS

The majority of ovarian cancer patients are in the age group of 40–60 years with an average age of 51 years. Patients who do not work have the highest cases. Based on histopathological appearance, serous carcinoma is found to be the highest case. Most cases were diagnosed with stage IIIC. The majority of these cases underwent surgery plus chemotherapy. Ovarian cancer patients often come at an advanced stage because there are often no complaints at an early stage, so women should carry out regular periodic health checks.

DECLARATIONS

Competing interest

The authors declare no competing interest in this study.

Ethics approval and consent to participate

This research was conducted after obtaining ethical approval from the ethics committee of Dr. Ramelan Navy Hospital Surabaya with number 68/EC/KEP/2022.

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