ORIGINAL ARTICLE

Characteristics of ovarian malignancy in Bali province, Indonesia

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ABSTRACT

Introduction: The aim of this study was to describe the characteristics of ovarian cancer (OC) diagnosed in a tertiary referral centre in Bali, Indonesia, according to several risk factors.

Materials and Methods: This is a descriptive retrospective study using data from the medical records of patients diagnosed with primary OC who underwent surgery at the Department of Obstetrics and Gynecology, Sanglah General Hospital Denpasar, Bali from January 2018 to December 2019.

Results: A total of 94 OC or 19.4% from total gynecologic cancer (484 cases) were diagnosed. The characteristics of the majority of OC were as follows: 1. Socio demography: median age 46.5 years (*interquartile range*: 16.5) and 47.9% (45/94) had low educational level; 2. Hormonal factor: 48.9% (46/94) were multiparous, 59.6% (56/94) were premenopausal, and 97.9% (92/94) had never used oral contraceptive pills; 3. Genetic: all patients did not have a family history of ovarian cancer; 4. Clinical characteristics: 76.6% (72/94) with histologic type of epithelial tumors, 61.7% (58/94) with advanced stage, 74.5% (70/94) with unilateral tumor, and 44.7% (42/94) with mass sized 11-20 cm. In advanced OC, 63.8% (37/58) presented with ascites and omental carcinomatosis, 87.9% (51/58) without liver metastasis; and 5. Surgical outcome: 55.3% (52/94) underwent primary cytoreductive surgery and 78.8% (41/52) had suboptimal surgical outcome.

Conclusions: The characteristics of OC in the study population were different compared with the developed countries and the global population, i.e. the incidence of OC was most common among younger and premenopausal women. The majority of patients with advance OC had suboptimal surgical outcome.

KEYWORDS:
Primary ovarian cancer, developing country, characteristics

INTRODUCTION

In 2018 worldwide? approximately 4.4% of cancer-related mortality in women was attributed to ovarian cancer (OC).[1] Although the prevalence of OC is lower than breast cancer, it is three times deadlier.[2] It has been known that there isappears to be a? geographical variation in the incidence, clinical characteristics, morbidity and mortality rate of OC. In developed countries, the incidence is significantly higher than in developing countries. However, the 5-years survival rate for all stages OC in developed countries has been increasing from 33.6% in 1975 to 44.2% in 2003-2009 and to 48.6% in 2010-2016.[3] The incidence of OC also varies according to age groups and race.[4] It is estimated that 30% of OC occurs in European countries.[5] Among the Asian countries, the highest incidence was found in Singapore, Kazakhstan, and Brunei Darussalam, respectively.[6]

The geographical variation in the incidence, clinical characteristics, morbidity and mortality rate of OC are attributed to the difference in the risk profile of patients, socioeconomic status, and access to the medical care. In countries with higher human development index (HDI), the incidence of OC is also higher but however, the mortality is lower.[6] Understanding the difference in risk profile and clinical characteristics of OC patients can assist in the efforts in prevention, early detection and treatment. Thus, data from specific population or geographical area is needed.

Indonesia is a developing country in the South East Asian region with a total population of over 270 million. The life expectancy at birth for Indonesian female is 73.7 years.[7] Published reports on epidemiologic data of OC among Indonesian women is still lacking. This study is aimed at describing the epidemiology of OC among Indonesian women.

MATERIALS AND METHODS

This is a descriptive, retrospective study involving all cases of OC diagnosed within the period of January 2018 to December 2019 in Sanglah General Hospital. Sanglah General Hospital is a tertiary referral hospital in the capital city of Denpasar, Bali Province, Indonesia, that serves as gynecologic oncology referral centre for Bali and Nusa Tenggara region. The inclusion criteria were all newly diagnosed cases of primary OC proven by official histopathology reports and recorded within the study period. The exclusion criteria were cases with incomplete data. Two cases with incomplete data (CA 125 level and the presence of liver metastasis) were excluded. Data regarding the socio demographics (age, educational

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Table I: Sociodemographic and clinical characteristic of the study population

Characteristics	N	%
Age group		
11-20 years	6	6.4
21-30 years	10	10.6
31-40 years	15	16.0
41-50 years	31	33.0
51-60 years	24	25.5
>60 years	8	8.5
Educational level		
Low	45	47.9
Moderate	43	45.7
High	6	6.4
Occupation		
Unemployed/housewives	39	41.5
Self-employed	35	37.2
Private employee	16	17.0
Medical personnel	2	2.1
Government officer	2	2.1
Histologic type		
Epithelial	72	76.6
Germ cell	18	19.1
Sex cord stromal	4	4.3
Stage		
I	19	20.2
II	17	18.0
III	51	54.4
IV	7	7.4
Bilaterality		
Yes	24	25.5
No	70	74.5
Tumor size		
≤ 10 cm	17	18.1
11-20 cm	42	44.7
21-30 cm	26	27.7
>30 cm	9	9.6
Total	**94**	**100**

Table II: Clinical characteristics of the advanced ovarian cancer

Characteristic	N	%
Histologic type		
Epithelial	44	75.9
Germ cell	11	19.0
Sex cord stromal	3	5.1
Bilaterality		
Yes	20	34.5
Tumor size		
≤ 10 cm	13	22.4
11-20 cm	28	48.3
21-30 cm	13	22.4
>30 cm	4	6.9
Ascites		
Yes	37	63.8
Omental carcinomatosis		
Yes	37	63.8
Liver metastasis		
Yes	7	12.1
CA125 level		
≤500 IU/ml	35	60.3
>500 IU/ml	23	39.7
Total	**58**	**100**

Table III: Critically ill patients' care after primary cytoreduction

Characteristics	N	%
ICU (Intensive Care Unit)		
With ventilator	15	28.8
Without ventilator	18	34.7
HCU (High Care Unit)	7	13.5
Ward	12	23
Total	**52**	**100**

Table IV: Treatment after primary cytoreduction

Characteristics	N	%
Chemotherapy 6 series (Adjuvant)	11	21.2
Immunotherapy	0	0
Radiotherapy	0	0
Second look laparotomy	15	28.8
Palliative setting		
Medically unfit to do second look surgery	9	17.3
Refuse to do second look surgery	7	13.4
Progressive disease	10	19.3
Total	**52**	**100**

level, occupation), hormonal factors (parity, menopausal status, use of oral contraceptive pills), genetic factors (family history of ovarian cancer), clinicopathology (histologic types, stages, laterality, sizes, ascites, omental carcinomatosis, liver metastasis), type of surgery, and surgical outcome were all extracted from the medical records. Information about family history of OC in the first and second degree relatives was obtained from a thorough history taking during the initial visit at the outpatient clinic or confirmed through telephone calls within the during the study period. Surgical outcomes after primary cytoreduction was defined using the criteria from Gynecologic Oncology Group and categorized as optimal if there was no residual mass (R0) or mass <1 cm after cytoreduction and suboptimal if there was residual mass >1 cm after cytoreduction.[8] The presence of ascites, omental carcinomatosis, and liver metastasis was inferred from findings on imaging (ultrasonography or abdominal CT) as well as the intraoperative evaluation by the gynecologic oncology surgeons? and confirmed by the histopathologic evaluation. The minimal volume of ascites that was defined as a significant marker of advanced ovarian cancer was set to be 500 ml. Data were analyzed using SPSS version 24.0.

This study was approved by the Institutional Review Board of Faculty of Medicine, Udayana University/Sanglah General Hospital, Denpasar, Bali, Indonesia (Ethical Clearance No. 1833/UN14.2.2.VII.14/LT/2020).

RESULTS

A total of 484 new cases of gynecologic cancer were diagnosed in our center in 2 years. OC accounted for 19.4% of the total cases (94/484) and all cases were referred cases from satellite hospitals within and outside Bali Province, Indonesia.

Sociodemographic

The median age of patients with OC in our centre was 46.5 years (IQR: 16.5 years). Age group of 41-50 years was the most common in which OC was diagnosed. Majority of the patients in the low socioeconomic status (Table I). Healthcare was accessible to all patients, including the primary health care that were available in every village. However, majority of the patients (76%) felt reluctant to seek advice from the medical professionals in a health care setting.

Hormonal and genetic factors

Median number of parities in our study population was 1.0 (IQR: 3.0). The proportion of nulliparous, primiparous and multiparous women were 36.2% (34/94), 14.9% (14/94) and 48.9% (46/94), respectively. Postmenopausal women only constituted 40.4% (38/94) of the total cases. Only two patients reported the use of oral hormonal contraceptives in the past (2.1%). No patient reported the family history of OC (first- or second-degree relatives).

Clinical characteristics

Abdominal enlargement was the most common symptoms present in this population (55/94 patients, 58.5%), followed by loss of weight (50/94, 53.2%), bloating (30/94, 31.9%), and abdominal pain (21/94, 22.3%).

Epithelial OC was the most common histologic type diagnosed in our center (76.6%). The distribution of epithelial subtype was as follows: 26 cases of serous carcinoma (27.7%), 15 cases of mucinous carcinoma (16.0%), 13 cases of clear cell carcinoma (13.8%), 11 cases of endometrioid carcinoma (11.7%), 5 cases of mixed epithelial tumor (5.3%) and 2 cases of undifferentiated type tumor (2,1%). Among the non-epithelial type, immature teratoma was the most common type (10/94, 10.6%), followed by germ cells tumor (mixed germ cells: 3/94, 3.2%; endodermal sinus or yolk sac tumor 3/94, 3.2%; dysgerminoma: 2/94, 2.1%), and sex cord stromal tumor (adult granulosa cell tumor: 2/94, 2.1%; malignant Sertoli-Leydig cell tumor: 1/94, 1.0%; mixed sex cord stromal cell tumor: 1/94, 1.0%).

Most cases were diagnosed in the advance stage, had unilateral mass, and sized 11-20 cm. Most of all types of

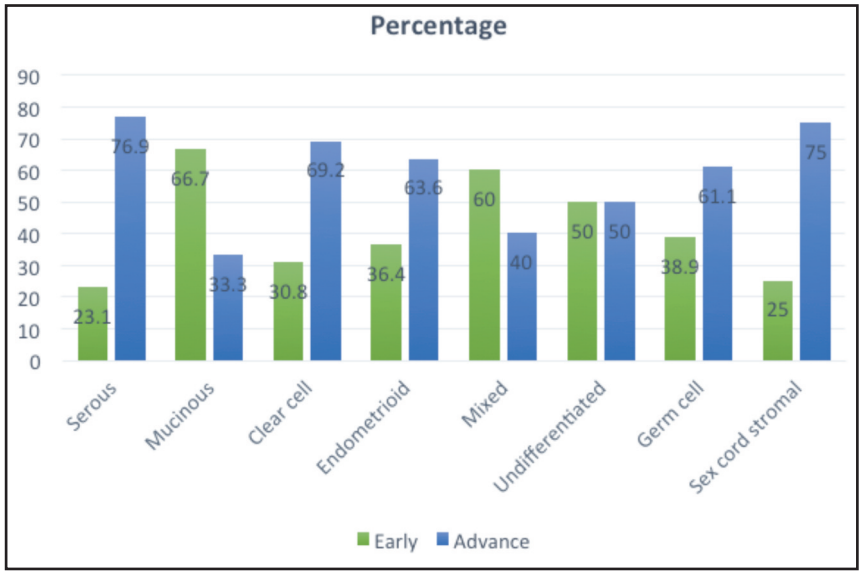

Fig. 1: A repeated CT scan of the neck showing compressed thrombus in the left internal jugular vein (blue arrow) with multi-loculated abscess measuring 2.1 x 1.9 x 2.5 cm (red arrow). Trachea is displaced to the right.

histology were diagnosed in advance stages (Figure 1). The clinical characteristics of advanced OC are summarized in Table II.

A total of 52 cases (55.3%) underwent primary cytoreductive or debulking procedure, while 27 cases (28.7%) underwent complete surgical staging, 8 cases (8.5%) underwent conservative surgical staging, and 7 cases (7.4%) underwent tumour biopsy. Among the cases that underwent primary cytoreduction, 8 cases (15.4%) were in stage IIB, 2 cases (3.8%) in stage IIIB, 36 cases (69.2%) in stage IIIC, and 6 cases (11.5%) in stage IVB. Among those who underwent primary cytoreductive, 41 cases (78.8%) had suboptimal outcome.

Post-operative care of critically ill patients and treatment after primary cytoreductive are as table III and table IV.

Transfusion facilities in our hospital are as part of Indonesia Red Cross Organization. This institution could facilities transfusion for emergency situation in 15-30 minutes.

Seven patients underwent laparotomy biopsy, three patients were given neoadjuvant chemotherapy for three series, followed by interval debulking. Due to medically unfit condition four patients underwent symptomatic palliative treatment.

For suboptimal cases after primary cytoreductive were given three cycle of chemotherapy and performed evaluation. Patients who were eligible to undergo operation, were continued with second look laparotomy. In the case of progressive disease, symptom palliative treatment was done, whether medical or operative, based on primary cause of the symptoms.

DISCUSSION

In this study, OC contributed to 19.4% of the total new cases of gynecologic cancer diagnosed within the two year period. During the study period, OC contributed to 17.0% of total new cases of gynecologic cancer in Indonesia.[9] It was the second commonest type of gynecologic cancer after cervical cancer (68.4%) but much more prevalent than endometrial cancer (8.5%), gestational trophoblastic neoplasia (3.9%), vulvar cancer (1.5%) and vaginal cancer (0.6%). This finding differs from the epidemiologic pattern seen in developed countries. For example, in the United States of America (USA), OC was more common than cervical cancer. There were 24.469 new cases of OC in 2018, as compared to 14.046 new cases of OC.[10] The higher incidence of OC in developed countries may be attributed to higher socioeconomic level, and thus, better access to healthcare services including early detection of.[6]

OC was commonly diagnosed in the age group of 41-50 years in our study population. Modi et al reported the same findings in India, where 46.2% of OC was diagnosed in the age group of 41-50 years.[11] However, data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry reported that the mean age of OC patients in USA during 2004-2014 was 53.5-64.7 years.[12,13] Global data shows that the median age at the time of diagnosis for OC is 50-79 years.[1] Thus, OC was diagnosed at a relatively younger age in our study population. The similar figures were reported by Modi et al in India might strengthen the fact that OC tends to occur in younger age groups in developing countries.

More than 40% of patients in our study population were in the low socioeconomic level. Indonesia is a developing country with moderate human development index (HDI) level. There was a positive and significant correlation between HDI level and the incidence of OC.6 However, HDI level did not correlate with the mortality due to OC. Alberg et

al.,[14] reported that there was a negative association between the educational level and the risk of OC. The lower socioeconomic level also correlated with more severe morbidity of OC.[15]

The peak incidence of ovarian cancer among Caucasian women occurs in the postmenopausal age.[1] However, among the Asian women OC tends to exhibit a different trend. Shen et al reported that among Chinese women, the prevalence of OC in the premenopausal group was 46%.[16] In our study, the prevalence of OC in the premenopausal group was 59.6%. This? number was relatively higher than the Caucasian women. The reason for the difference may be due to the racial difference in the genetic susceptibility for OC. Han et al reported that genetic polymorphism (rs6983267 in chromosome 8q24) among Chinese women increases the risk for OC in the premenopausal age group (adjusted OR=1.62, 95% CI:1.18-2.23, P = 0.003).[17]

More than 20% of OC are hereditary in origin.[18] Approximately 65-85% cases of hereditary OCare associated with BRCA mutation. Mutation of other tumor suppressors or oncogenes are also involved in the pathogenesis of OC, such as mutation of TP53, BARD1, CHEK2, RAD51 dan PALB2. Lynch syndrome contributes to 10-15% of hereditary OC.[19] In this study, no patients reported a family history of OC. Genetic testing for OC risk is still a very rare option offered in this population. In fact, information about genetic testing is seldomly discussed by the healthcare professionals. However, some physicians will offer genetic testing if the patients present with a strong family history of ovarian or breast cancer. Studies evaluating the epidemiology of genetic susceptibility for OC among Indonesian women are also lacking.

Epithelial OC was the most common histologic type in this study, followed by germ cell tumour and sex cord stromal tumour, respectively. Patel et al[20] report the same distribution pattern of OC in India. Serous carcinoma was the most common type of epithelial OC in this study. This is in accordance to the study reported by Modi et al[11], Gupta et al[21], and Yogambal et al[22] in India. Data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry in USA during 2004-2014 reported that high-grade serous carcinoma was the commonest type of epithelial ovarian cancer (63.4%), followed by endometrioid carcinoma (9.9%), clear cell carcinoma (9.6%), mucinous carcinoma (9.4%), carcinosarcoma (4.9%), low-grade serous carcinoma (2.5%), and malignant Brenner tumors (0.3%).[12] Although there is a difference in the risk profile of OC, the distribution of histologic type seems to be similar between our population and the global population.

In this study, the more than half of epithelial OC were diagnosed at the advance stage. The same observation was also found for germ cell and sex cord stromal ovarian tumour. Among the epithelial OC diagnosed in our study, serous, clear cell, and endometrioid type of OC were diagnosed in advance stage while mucinous carcinoma was diagnosed in the early stages. Data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry in 2004-2014 also reported the same pattern of distribution.[12] Recent data from the 2018 National Center for Health Statistics registry in the USA reported that mucinous carcinoma tend to be diagnosed in the advance stages while germ cell and sex cord stromal ovarian tumour were diagnosed at early stage.[4] Advance stage at diagnosis is associated with late recognition of OC. More importantly, there is often a long waiting time before primary treatment (months, rather than weeks), which might be too long for this kind of tumours. In developing countries, other factors that may also contribute to the more advance stage at diagnosis are lower socioeconomic levels.

As for the advance stage OC diagnosed in this study, majority of cases were epithelial type, with unilateral tumor, ascites and omental carcinomatosis. The median size of tumour at presentation was 20 cm (IQR:15.0 cm). Only a small portion of cases present with liver metastasis or CA125 level above 500 IU/ml. Chesnais et al.,[23] reported in their study that the proportion of advance OC patients who presented with ascites was 60.7%, while those who presented with omental carcinomatosis was 40.5% and liver metastasis was 24.3%. Many studies have proposed that the presence of ascites, omental carcinomatosis, liver metastasis and high level of CA125 (>500 IU/mL) can predict the surgical outcomes for advanced OC.[23-28] It was reported that advanced OC with ascites, omental carcinomatosis, liver metastasis and high level of CA125 tend to have suboptimal outcome after cytoreductive surgery.[23,24,28] In this study, the proportion of advanced OC patients who presented with ascites and omental carcinomatosis was quite high (>50%). However, hospital related factors such as availability of adequately trained staff, operating theatres and ICU facilities as well as waiting lists were also the important factors determining the outcomes of patients. In our hospital, the waiting list can be as long as one month.

Majority of cases in our study underwent primary cytoreductive surgery (55.3%), while a small proportion underwent conservative surgical staging (8.5%). The majority of those who underwent cytoreductive surgery had suboptimal outcome (78.8%). A lower percentage of suboptimal outcome was reported in a study by Chesnais et al23 in France (62.3%) and Rosendahl et al[29] in Denmark (50%). Suboptimal outcome is correlated with the larger extend of tumour spreading.[23] It has been widely accepted that residual mass after cytoreductive surgery is one of the most important prognostic factor for OC.[30] An increase in the proportion of patients who achieved optimal cytoreduction as minimal as 10% was a significant and independent predictor for an increase in medial survival for 1.8 months (95% CI 0.6-3.0, p=0.004).[8] Clinical predictors for surgical outcome of advanced OC would be beneficial in developing countries where costly imaging modalities (e.g., CT, PET scan) or laparoscopy are not widely available.

Important achievements have been made in terms of targeted therapies in the management of OC, including in cases after debulking surgery. In Indonesia, addition of targeted therapy is an option for the patient. Moreover, the treatment is not yet covered by national insurance program and to benefit from this targeted therapy, we should continue our efforts to identify and testing patients who are may potentially benefit from targeted therapy.

We are aware that tertiary hospitals like our hospital have a highly selected population of patients and their characteristics may differ considerably from the Indonesian national databases. However national data of OC that was based on population-based study is currently unavailable.

CONCLUSION

It is known that disease patterns like gynaecological cancers appear earlier in developing and under-developed countries because of the lack of screening tools, residing far from health facilities, transportation difficulties and financial strains in contrast to patients from the developed world.

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