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Epidemiology Profile of Stage IV Ovarian Cancer in Dharmais National Cancer Hospital: An Observational Study

Hilman Tadjoedin [1*], Kresna Dharma Suryana [1], Widyorini Lestari Hutami Hanafi [2], Manika Putri Kunigara [3], Alyssa Fairudz Shiba [3]

[1] Department of Hematology and Medical Oncology, Dharmais Cancer Hospital - National Cancer Center, Jakarta, Indonesia
[2] Department of Obstetric and Gynecology, Division of Gynecology Oncology, Dharmais Cancer Hospital - National Cancer Center, Jakarta, Indonesia
[3] Research Assistant, Department of Hematology and Medical Oncology, Dharmais Cancer Hospital - National Cancer Center, Jakarta, Indonesia

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ABSTRACT

Background: Stage IV ovarian cancer showed a low 5-year survival rate, around 31%. Regrettably, the unclear symptoms and the ineffectiveness of early detection result in many patients being diagnosed with stage IV. Moreover, establishing a stage IV diagnosis is challenging and tricky. This study aims to provide a comprehensive overview of the clinical, laboratory, histopathological, and survival characteristics of stage IV ovarian cancer patients.

Method: A cross-sectional study with a descriptive observational design, 100 of 1520 subjects gathered from the Cancer Registry of Dharmais National Cancer Hospital between January 2018 and December 2022, conducted on stage IV ovarian cancer patients who were not accompanied by primary cancer at other sites.

Results: Among the 100 study subjects, 76.0% were aged 40–60 years, with a median age of 49.5 years. Most had a normal nutritional status (39.0%) or were underweight (34.0%). Comorbidities were present in 40.0% of the subjects, with hypertension being the most common (57.5%). The initial symptoms were abdominal enlargement in 74.0% of subjects, with 43.0% reporting shortness of breath. Laboratory examinations revealed that the majority had hemoglobin levels > 10 mg/dL (90.0%), serum creatinine levels < 1.2 mg/dL (90.0%), and D-Dimer levels > 2000 ng/mL (69.0%). Histopathological analysis identified high-grade serous carcinoma (HGSC) in 24.0% and clear cell carcinoma in 19.0% of subjects. The most common metastatic sites were the pleura (44.0%), liver (41.0%), and lungs (25.0%). Around 48.0% and 41.0% had surgery only and surgery with adjuvant chemotherapy, respectively. The majority of the outcomes (91.0%) indicated that patients with stage IV ovarian cancer did not survive and the median survival among the subjects was 4 months.

Conclusion: The majority of stage IV ovarian cancer patients were aged 40–60 years, with abdominal enlargement as the initial symptoms, elevated D-Dimer levels, HGSC as the predominant histopathological type, and a high mortality rate as the outcome. Further research is recommended to explore additional variables and analyze factors contributing to mortality.

*Corresponding Author:
Hilman Tadjoedin
Department of Medical Hematology Oncology, Dharmais National Cancer Hospital, Indonesia
htadjoedin13@gmail.com

INTRODUCTION

Ovarian cancer is a leading gynecological malignancy with a high incidence rate and is the third most common cause of death among gynecological cancers, despite being treated by advanced therapeutics [1]. In Indonesia, there were 15,310 new cases of ovarian cancer, with 9,673 deaths [1]. Globally, there are approximately 324,603 new cases annually, with 206,956 deaths each year [1,2].

At stage IV, the five-year survival rate is low, approximately 31% [3]. The number of stage IV cases among ovarian cancer patients is still high [4]. The unclear symptoms and ineffective early detection contribute to the late diagnosis of ovarian cancer, leading to many cases being diagnosed in stage IV [5–7]. In Indonesia, stage IV ovarian cancer is most commonly diagnosed in patients aged 40–60 years [8,9]. In contrast, data from the National Cancer Institute (NCI) indicate that the majority of stage IV cases in the Asian population occur in individuals aged 65–74 years [10]. However, the histopathological findings of ovarian cancer patients in Indonesia and abroad show a consistent pattern, with the serous subtype being the most prevalent [8,9,11]. Moreover, establishing a stage IV diagnosis is challenging and tricky. Diagnosis establishment of ovarian cancer staging can be done based on clinical examination (anamnesis of complaints, physical examination, laboratory, radiology) and histopathology examination [12]. Management of FIGO stage IV ovarian cancer is recommended to perform hysterectomy and bilateral-salpingo oophorectomy (BSO) or neoadjuvant chemotherapy followed by interval debulking surgery (IDS), then continued with adjuvant therapy [12].

As a national referral hospital for cancer patients, Dharmais National Cancer Hospital has not yet provided data on the characteristics of stage IV ovarian cancer patients. This study aims to fill that gap by providing a comprehensive overview of these patients, which could serve as a foundation for future research and policy-making regarding ovarian cancer.

METHODS

This is a cross-sectional study with descriptive methods. The data was obtained from the cancer registry between January 2018 and December 2022. The population was ovarian cancer as the reason for referral or diagnosis first time at Dharmais Cancer Hospital (1519 subjects). The subjects included in this study were patients aged > 18 years with stage IV ovarian cancer confirmed by histopathology results. Patients with ovarian cancer accompanied by primary cancer at other sites were excluded from the study. The calculation of the number of samples used the Slovin formula with sampling using the total sampling method so that 100 of 1519 subjects were included in this study. Data collection was carried out in June 2024. The variables in this study consisted of clinical characteristics including age, body mass index (BMI), nutritional status, comorbidities, type of comorbidity, and main complaints which were seen from the medical records when the patient first came, laboratory findings (hemoglobin levels, serum creatinine levels, and D-Dimer levels) which were first obtained before the patient received chemotherapy/ underwent surgery, histopathology (cell type and metastatic sites), treatment profile, survival time, and outcome (death/alive).

Descriptive analysis was conducted using SPSS Statistics 23.0 to calculate case incidence, with results presented as percentages. Some variables were also presented as mean, standard deviation, median, minimum, and maximum values. We analyze median survival using Kaplan-Meier.

RESULTS

Clinical Characteristics

From 2018 to 2022, 100 subjects met the inclusion and exclusion criteria. The distribution of clinical characteristics is presented in **Table 1**. The majority of subjects were aged 40–60 years (76.0%), with the least number of subjects aged < 40 years (14.0%). The average and median ages were 50.5 and 49.5 years, respectively. The BMI distribution, based on the WHO classification for the Asian population, showed that 39 subjects (39.0%) had normal BMI, 34 subjects (34.0%) were underweight, 15 subjects (15.0%) were obese, and 12 subjects (12.0%) were overweight. The average and median BMI were approximately 20.4 kg/m2. According to the European Society for Clinical Nutrition and Metabolism (ESPEN), 56 subjects (56.0%) were moderately malnourished. The three most common initial symptoms leading patients to seek medical attention were abdominal enlargement (74.0%), shortness of breath (43.0%), and abdominal pain (24.0%). Comorbidities were present in 40 subjects (40.0%), with hypertension being the most common (57.5%), followed by cardiovascular disease (28.3%), diabetes mellitus (10.0%), hepatitis (7.5%), tuberculosis or cerebrovascular disease (2.5% each), and other comorbidities (5.0%).

Laboratory Characteristics

The distribution of laboratory results is presented in **Table 2**. Based on hemoglobin levels, 90.0% of subjects had Hb > 10 mg/dL, and 10.0% had Hb < 10 mg/dL. Serum creatinine levels were < 1.2 mg/dL in 90.0% of subjects and > 1.2 mg/dL in 10.0% of subjects. D-Dimer levels were > 2000 ng/mL in 69.0% of subjects and < 2000 ng/mL in 12.0% of subjects.

Histopathological Characteristics

Histopathological examination results in this study were varied (**Table 3**). The majority were high-grade serous carcinoma (HGSC) in 24 subjects (24.0%), followed by clear cell carcinoma in 19 subjects (19.0%), adenocarcinoma (14.0%), endometrioid carcinoma in 13 subjects (13.0%), and mucinous carcinoma in 13 subjects (13.0%). The most frequent metastatic locations were the pleura in 44 subjects (44.0%) and the liver in 41 subjects (41.0%). The least frequent metastatic location was the skin, with only 1 subject (1.0%).

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Table 1. Clinical characteristics

Variable	n (%)	Mean ± SD	Median (Min-max)
Age		50.5 ± 10.5	49.5 (18–75)
< 40	14 (14.0)		
40–60	76 (76.0)		
> 60	10 (10.0)		
Body mass index (kg/m^2)		20.4 ± 3.9	20.40 (13.3–29.2)
Underweight (< 18.5)	34 (34.0)		
Normal (18.5–22.9)	39 (39.0)		
Overweight (23–24.9)	12 (12.0)		
Obesity (≥ 25)	15 (15.0)		
Nutritional status			
Severe Malnutrition	18 (18.0)		
Moderate Malnutrition	56 (56.0)		
Normal	26 (26.0)		
Comorbidity			
Yes	40 (40.0)		
No	60 (60.0)		
Type of comorbidities (n = 40)			
Hypertension			
Yes	23 (57.5)		
No	17 (42.5)		
Cardiovascular disease			
Yes	17 (28.3)		
No	23 (57.5)		
Diabetes mellitus			
Yes	4 (10.0)		
No	36 (90.0)		
Cerebrovascular disease			
Yes	1 (2.5)		
No	39 (37.5)		
Tuberculosis			
Yes	1 (2.5)		
No	39 (37.5)		
Hepatitis			
Yes	3 (7.5)		
No	37 (32.5)		
Other comorbidities			
Yes	2 (5.0)		
No	38 (95.0)		
Initial symptoms (n = 100)			
Abdominal enlargement			
Yes	74 (74.0)		
No	26 (26.0)		
Shortness of breath			
Yes	43 (43.0)		
No	57 (57.0)		
Abdominal pain			
Yes	24 (24.0)		
No	76 (76.0)		
Defecation/urinary disorder			
Yes	8 (8.0)		
No	92 (92.0)		
Nausea/vomiting			
Yes	1 (1.0)		
No	99 (99.0)		
Other symptoms			
Yes	2 (2.0)		
No	98 (98.0)		

SD: Standard Deviation

Table 2. Laboratory characteristics

Variable	n (%)	Mean ± SD	Median (Min-max)
Haemoglobin (mg/dL)		11.6 ± 7.5	10.9 (6.3–84.0)
< 10	10 (10.0)		
≥ 10	90 (90.0)		
Creatinine Serum (mg/dL)		0.9 ± 0.6	0.8 (0.3–5.2)
< 1.2	90 (90.0)		
≥ 1.2	10 (10.0)		
D-dimer (ng/mL)		10,193.3 ± 10,139.1	6,800 (290–54,000)
< 2,000	12 (12.0)		
> 2,000	69 (69.0)		
Missing	19 (19.0)		

Table 3. Histopathological characteristics

Variable	n (%)
Histopathology Result	
High-grade serous carcinoma	24 (24.0)
Clear cell carcinoma	19 (19.0)
Endometroid carcinoma	13 (13.0)
Mucinous carcinoma	13 (13.0)
Adenocarcinoma	14 (14.0)
Adult granulosa cell tumor	4 (4.0)
Serous cystadenocarcinoma	3 (2.6)
Low-grade serous carcinoma	2 (2.0)
Yolk sac tumor	2 (2.0)
Brenner tumor	1 (1.0)
Leiomyosarcoma	1 (1.0)
Ovarian squamous cell carcinoma	3 (3.0)
Papillary serous carcinoma	1 (1.0)
Metastatic Location	
Pleura	
Yes	44 (44.0)
No	56 (56.0)
Liver	
Yes	41 (41.0)
No	59 (59.0)
Lung	
Yes	25 (25.0)
No	75 (75.0)
Bone	
Yes	11 (11.0)
No	89 (89.0)
Gastrointestinal – Genitourinary	
Yes	10 (10.0)
No	90 (90.0)
Brain	
Yes	2 (2.0)
No	98 (98.0)
Spleen	
Yes	5 (5.0)
No	95 (95.0)
Distant lymph node	
Yes	4 (4.0)
No	96 (96.0)
Skin	
Yes	1 (1.0)
No	99 (99.0)

Table 4. Treatment characteristics

Variable	n (%)
No surgery or chemotherapy	6 (6.0)
Surgery only	48 (48.0)
Neoadjuvant chemotherapy with surgery	5 (5.0)
Surgery with adjuvant chemotherapy	41 (41.0)

Table 5. Outcome characteristics

Outcome	n (%)
Death	91 (91.0)
Survive	9 (9.0)

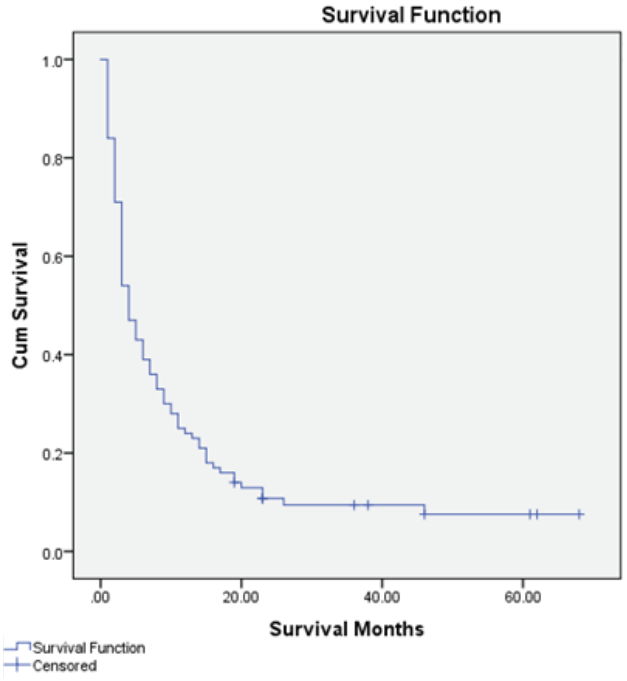

Figure 1. Overall survival of stage IV ovarian cancer

Treatments

Management of stage IV ovarian cancer patients at Dharmais Cancer Hospital consists of no surgery or chemotherapy, surgery alone, neoadjuvant chemotherapy, and surgery with adjuvant chemotherapy. Among 48% of patients did surgery and 41% did surgery with adjuvant chemotherapy (**Table 4**).

Outcomes

The most common outcome was mortality (**Table 5**), with almost all subjects (91.0%) dying during the study period, and only 9 subjects (9.0%) surviving. By the Kaplan-Meier analysis, the median survival was 4 months (**Figure 1**).

DISCUSSION

The average and median ages of stage IV ovarian cancer patients at Dharmais Cancer Hospital were 50.25 and 49 years old, respectively, with the majority (74.8%) aged 40–60 years. Previous studies at Cipto Mangunkusumo National Central General Hospital in 2002 reported that 26.8% of patients were aged 45–54 years [13], and in 2007, 53.9% were aged 40–60 years [8]. Similarly, a study at Dr. Ramelan Navy Hospital Surabaya showed that 52.9% of patients were aged 40–60 years with an average age of 51 years [9]. In contrast, studies conducted in the United States reported a higher average age of 60.1 years [14]. The age difference could be due to limited access to health facilities, especially gynecological examinations in Indonesia, consequently, ovarian cancer was detected in stage IV at a younger age.

Regarding BMI classification based on WHO criteria, the majority of patients were either normal weight (37.4%) or underweight (35.7%), with a smaller proportion being obese (15.7%) or overweight (11.3%) upon initial hospital admission. A study conducted in California found that obesity in stage IV ovarian cancer patients was associated with increased survival rates [15], this is likely because cancer patients almost present cachexia, a syndrome characterized by loss of muscle with or without loss of fat mass which leads to weight loss and reduced BMI (below 20 kg/m2) [16]. The mean and median BMIs in this study were approximately 20.4 kg/m², indicating a normal nutritional status. Similarly, Gunawan et al. reported an average pre-chemotherapy BMI of 22.86 kg/m², also classified as normal nutritional status [17].

In this study, 39.1% of subjects had comorbidities, with hypertension and cardiovascular disease being the most prevalent (**Table 1**). A cross-sectional study in France reported similar findings, with one-third of ovarian cancer patients having comorbidities, primarily vascular diseases [18]. However, other studies indicated that cardiovascular disease ranked third, with the most common comorbidity being tumors at other sites [19]. Tetsche et al. [19] analyzed the relationship between the severity of comorbidities (calculated using the Charlson Comorbidity Index Score) and stage IV ovarian cancer. The parameter of this comorbidities index considers age and the presence of several diseases such as the history of myocardial infarction, heart failure, peripheral vascular disease condition, cerebrovascular accident or transient ischemic attacks, dementia, chronic obstructive pulmonary disease (COPD), connective tissue disease, peptic ulcer disease, the severity of liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, and Acquired Immunodeficiency Syndrome (AIDS) [20]. The results showed that severe comorbidities (Charlson score of 3) were associated with stage IV cancer [19]. The presence of comorbidities has also been linked to decreased survival rates in cancer patients, suggesting that clinicians should consider comorbidities when determining cancer therapy to avoid worsening or inducing side effects related to these conditions [21,22].

The initial symptoms that led patients to consult a doctor were abdominal enlargement (73%), shortness of breath (42.6%), and abdominal pain (21.7%). A study by Dilley et al. [6] in the United Kingdom reported that abdominal/pelvic pain and abdominal distension were the most common complaints in ovarian cancer patients, at 39.5% and 29.2%, respectively. Interestingly, Dilley et al. [6] also noted that about 2.3% of patients presented asymptomatic. Similarly, Matsuo et al. [23] in California reported that abdominal pain (40.6%) and abdominal distension (33.7%) were the most frequent symptoms in ovarian cancer patients. Meena et al. [24] in North India reported findings consistent with this study, noting abdominal enlargement as the most common initial symptom.

The mean and median hemoglobin levels upon initial hospital presentation were 11.3 mg/dL and 10.8 mg/dL, respectively (**Table 2**). Gunawan et al. [17] at Cipto Mangunkusumo Hospital reported that hemoglobin levels in stage IV epithelial ovarian cancer patients ranged from 8 to 13 mg/dL, with the majority (95.65%) having Hb > 10 mg/dL. These findings are similar to this study, where 66.1% of stage IV ovarian cancer patients had Hb > 10 mg/dL. These Hb level results are likely due to the examination conducted before the patient received chemotherapy or underwent surgery. A study by Gunawan et al. [17] showed a decrease in Hb levels from an average of 11.30 mg/dL to 10.63 mg/dL after chemotherapy.

Serum creatinine (sCR) levels (**Table 2**) were predominantly < 1.2 mg/dL, with only 17.4% showing levels > 1.2 mg/dL. A study conducted in Bali, Indonesia, reported that the average sCR before chemotherapy was approximately 0.67 mg/dL, increasing to around

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0.78 mg/dL after chemotherapy [25]. A study in Austria reported similar findings, with only 4.4% of patients having sCR > 1.2 mg/dL. Elevated sCR levels were associated with poor survival rates [26]. This relationship may be due to malignancy itself or the adverse effects of chemotherapy drugs, such as niraparib or cisplatin [15,26,27]. In general, the chemotherapy regimen administered at Dharmais National Cancer Hospital for ovarian cancer patients is platinum-based, such as paclitaxel, carboplatin, bleomycin, etoposide, and platinum (BEP), oxaliplatin, and cisplatin. A study conducted in Bali, Indonesia, reported that the average sCR before chemotherapy was approximately 0.67 mg/dL, increasing to around 0.78 mg/dL after chemotherapy [25].

In this study, D-Dimer levels had an average of 12,619 ng/mL, with the majority of patients (84.8%) having D-Dimer > 2,000 ng/mL (**Table 2**). A study in Japan reported similar findings, indicating that D-Dimer levels > 1,500 ng/mL were associated with poorer overall survival compared to levels below this threshold. D-Dimer serves as a prognostic marker for overall survival, and it is highly recommended to measure D-Dimer levels before initiating therapy [28]. Increased D-Dimer in patients with cancer due to hypercoagulability and the occurrence of fibrinolysis as a consequence, can be caused by cancer-induced hypercoagulability, increased inflammatory cytokines, vascularization, or VTE [29,30].

Histopathological examination results showed that high-grade serous carcinoma (HGSC) was the most common type, found in 20% of subjects, followed by clear cell carcinoma (16.5%). Previous studies conducted in Indonesia reported similar findings [8,9]. International studies also indicate that the serous subtype is the most prevalent [6,14,31]. A study conducted in the United States highlighted a difference in the distribution of histopathological types between distant-stage and localized ovarian cancer. In distant-stage cases, serous carcinoma was the most common, whereas other subtypes were more prevalent in localized cases [14].

The most common metastatic sites in ovarian cancer were the pleura (42.6%), liver (40.9%), and lungs (7%), with the least common site being the skin (0.9%). A study by Deng et al. [31] in China reported that liver metastasis occurred in 37.5% of cases, followed by distant lymph nodes, lungs, bones, and the brain. Overall survival rates decreased respectively from lymph node metastasis, liver metastasis, to lung metastasis [31].

This study showed that the median survival of overall survival was 4 months. It is shorter than another study in Indonesia, a study from Dr. Cipto Mangunkusumo Hospital, the median survival was 31 months [32]. In the other country, Cyprus, the median survival of progression-free survival (PFS) in stage IV ovarian cancer was 13 months, the lowest among other stages (with 60 months for longest survival in stage I) [33]. A study from Japan, among ovarian stage IV ovarian cancer, showed different results between the serous-endometroid than others, 37 and 10 months, respectively [34]. This study resulted in patient awareness of their condition and the need for continued therapy remains limited, resulting in some ovarian cancer patients being lost to follow-up.

Almost all patients (92.2%) with stage IV ovarian cancer died during the study period. In contrast, the RESPONSE Trial, a multinational cohort study, reported different outcomes for newly diagnosed advanced ovarian cancer patients with a 20-month follow-up, where approximately 20.6% died, and the remaining experienced disease-free or progressive disease [35]. A study conducted in the United States reported that around 43.5% of stage III and IV ovarian cancer patients died within the first year after diagnosis, with the highest mortality (26%) occurring within the first 90 days post-diagnosis [28].

This study provides an overview of clinical, laboratory, histopathological, and survival characteristics of stage IV ovarian cancer patients at Dharmais National Cancer Centre, this study provides a critical baseline for future research in more in-depth.

This study has some limitations, some variables were difficult to obtain due to the transition from manual to electronic medical records during the study period. Future studies could explore variables such as age at menopause, parity rates, family history of malignancy, history of contraceptive use or hormonal therapy, and genomic profile. Additionally, this study was conducted at a single center; therefore, a multicentre study is recommended to provide a broader perspective. The high mortality rate observed in this study could serve as a foundation for further research to identify factors contributing to mortality.

CONCLUSIONS

Stage IV ovarian cancer patients are predominantly aged 40-60 years, have a normal BMI, and two-thirds present with comorbidities, primarily hypertension and cardiovascular disease. Most patients report abdominal enlargement at initial presentation. The most common histopathological subtype is high-grade serous ovarian cancer, with metastasis primarily to the pleura, followed by the liver, and the majority exhibit elevated D-dimer levels. Mortality stands at 91%, with a median survival time of 4 months. Further research will be conducted soon to analyze the factors causing death and survival.

DECLARATIONS

Ethics Approval

The ethical review of this research was approved, and the ethical clearance letter No. DP.04.03/11.7/029/2024 was obtained. No patient-identifying information was used because all data were anonymized.

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Competing Interests

The authors hereby declare that they have no competing interests.

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