Scientific Research Publishing

Journal of Cancer Therapy, 2023, 14, 416-428
https://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Epithelial Ovarian Cancer Patients and Clinicopathological Features and Survival: A Comparison of Outcomes of Two Age Cohorts in Bangladesh

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How to cite this paper: Haque, F., Pervin, S. and Goodman, A. (2023) Epithelial Ovarian Cancer Patients and Clinicopathological Features and Survival: A Comparison of Outcomes of Two Age Cohorts in Bangladesh. *Journal of Cancer Therapy*, **14**, 416-428.
https://doi.org/10.4236/jct.2023.1410035

Received: September 25, 2023
Accepted: October 23, 2023
Published: October 26, 2023

Abstract

Objective: This study compared the clinicopathologic characteristics and overall survival of epithelial ovarian carcinoma in women younger versus older than 45 years in Bangladesh. **Methods:** A retrospective analysis identified 129 epithelial ovarian carcinoma patients who were admitted to the National Institute of Cancer Research and Hospital, in Dhaka, Bangladesh from 2016 through 2017 for surgery. These patients were grouped into two categories: the younger group (≤45 years) and the older group (>45 years). Clinicopathological features of epithelial ovarian carcinoma were analyzed in each age group. Cox proportional hazards model identified factors affecting survival and Kaplan-Meier survival curves with log rank test compared outcomes for each age group. **Results**: The median age of the 129 women was 46 years (IQR: 38, 56) and median time of follow-up was 9 months (inter-quartile range: 4, 26.5). We found a significant difference in the CA-125 level ($p < 0.044$), age of menopause ($p < 0.001$), follow-up duration ($p < 0.016$), disease outcome ($p < 0.005$) and histopathological type ($p < 0.021$) between the two groups. No significant differences were found in breakdown of Federation of Gynecology and Obstetrics (FIGO) stage of the disease. There was a significant difference in overall survival between the patients of two groups ($p = 0.021$) where there was a higher probability of death among the older cohort. The 5-year overall survival rates for the younger age versus older group were 34.0%, and 11.7% respectively. Independent prognostic factors by univariate analysis for the overall survival were age, FIGO stage, preoperative CA-125 and CEA level. However, when controlling for stage, survival was similar between age cohorts. **Conclusions:** Our data suggests that women in Bangla-

desh with epithelial ovarian cancer who are under the age of 45 years have a different clinical profile and better overall survival than women in the older age cohort.

Keywords

Epithelial Ovarian Cancer, Age, Survival, Bangladesh

1. Introduction

Ovarian cancer is the seventh most common cancer in women throughout the world [1]. Epithelial ovarian cancer (EOC) with the subtypes high grade serous, low grade serous, mucinous, clear cell, and endometrioid comprises 95% of malignant ovarian neoplasms [2]. Epithelial ovarian cancer (EOC) is the foremost life-threatening genital tract malignancy among women in the world [3] [4]. EOC is diagnosed at late stages as earlier stages are asymptomatic and there is no effective screening test for early ovarian cancer [5] [6]. Survival is dependent on stage at diagnosis, tumor histology and adequate surgical treatment [6]. Most of these cancers are diagnosed in postmenopausal women aged 55 to 64 years with a median age of 63 years and a median age of death from ovarian cancer of 70 years [7]. Ten percent of EOC are diagnosed below 40 years of age [3] [7]. While 95% of women with early-stage epithelial ovarian cancer survive for 5 years [8], the overall 5-year survival rate is approximately 30% despite aggressive treatment including surgery and chemotherapy [3].

Data on the prognostic significance of age in outcomes for epithelial ovarian cancer is mixed. Chan *et al.* reported that younger women with EOC had better survival and prognosis compared to older patients [9]. In contrast, a multivariate analysis of Japanese EOC patients reported that early age was not an independent prognostic factor for OS [3]. Previous reports regarding age and outcomes for EOC patients come from the United States, European countries, and Japan [3] [10]. However, patients' clinical characteristics and access to comprehensive cancer care may vary between Western and Asian countries like Bangladesh.

There are no reports on the clinical characteristics of young EOC patients from Bangladesh and other South Asian countries and little is known about the effect of age on prognosis in this population. The objective of our study is to examine the impact of age on the clinicopathologic characteristics and overall survival (OS) of EOC in younger vs. older patients in Bangladesh.

2. Methods

2.1. Participants and Study Site

We conducted a retrospective analysis of 129 EOC patients who were admitted to the National Institute of Cancer Research and Hospital (NICRH), situated in

Dhaka, Bangladesh from 2016 through 2017 for surgery. We excluded the non-epithelial ovarian malignancy, dual malignancies and recurrent EOC cases in this analysis. EOC patients were diagnosed based on clinical and laboratory findings, supported by imaging reports (ultrasound and/or CT scan) and confirmed by histopathology. The Federation of Gynecology and Obstetrics (FIGO) staging system was used and women with FIGO stage I-IV EOC were enrolled in this study [11]. The patients were followed for five years after their initial diagnosis at NICRH. After completion of therapy, patients were examined every three to four months for the first three years and then every six months for two years. All EOC patients were grouped into two categories: a younger cohort (≤45 years) and an older cohort (>45 years).

2.2. Data Collection

Patients' demographic information, clinical signs and symptoms, tumors morphology, stage of tumors, tumor markers, findings of histopathology, surgical procedures, and follow-up were recorded using data collection forms at NIHCR after hospital admission of the patients. Information was obtained from paper medical records. Outpatient medical records were stored in the outpatient unit. A separate inpatient record which included operative notes was maintained on all patients admitted to the hospital. Operative notes were handwritten and briefly summarized the surgical procedures. Operation notes are preserved in the government register books which are present in the operation theater. Patients also carried a copy of all their medical medicals with them that included an outpatient treatment sheet, an investigations report, operative notes, a chemotherapy card, and any follow-up notes. The patient's personal medical record file was cross checked with the outpatient records when they came in for outpatient visits. Telephone numbers and addresses were recorded and kept in a record keeping book in the outpatient department. Patients who did not come for follow up visits were contacted over the telephone by one of the authors. If they were alive, they were encouraged to return to NICRH for a follow-up visit. If the patient had died, details of what had happened were obtained from family members.

2.3. Ethical Consideration

The ethical approval of this study was taken from the Institutional Review Board of NICRH.

2.4. Surgical Procedures

2.4.1. Staging Laparotomy

Ovarian epithelial malignancies are staged according to the FIGO system which is based on findings at surgical exploration. Surgical staging is usually done at early stage of disease [11]. Primary treatment for presumed ovarian, fallopian tube, or primary, peritoneal cancer usually consists of appropriate surgical staging and debulking surgery [12]. In this study, staging laparotomy included total

hysterectomy, bilateral salpingo-oophorectomy (BSO), infracolic omentectomy, pelvic peritoneal biopsies from vesico-uterine pouch, both paracolic gutters and from suspicious areas or adhesions and pelvic and para-aortic lymph node dissections.

2.4.2. Interval Debulking Surgery (IDS)

Neoadjuvant chemotherapy (NACT) with IDS should be considered for patients with advanced-stage ovarian cancer who are not good candidates for PDS due to advanced age, frailty, poor performance status, comorbidities, or who have disease unlikely to be optimally cytoreduced [13]. NACT is indicated for advanced staged ovarian cancer (FIGO stage lllC & lV) prior to cancer surgery which is intended to reduce the tumor burden in preparation for surgery [12]. At our hospital, total hysterectomy with BSO, omentectomy and sometimes unilateral salpingo-oophorectomy and omentectomy were done in cases of interval debulking surgery.

2.4.3. Primary Debulking Surgery (PDS)

Primary debulking surgery (PDS) is performed for advanced staged surgically resectable disease where the removal of the primary tumor as well as the associated metastatic disease is possible [11]. At our center, we performed total hysterectomy, bilateral salpingo-oophorectomy, omentectomy along with resection of any metastatic lesions from the peritoneal surfaces or from the intestines which included resection of rectosigmoid colon, appendectomy, large intestinal resection, small bowel resection and partial gastrectomy.

2.5. Statistical Analysis

The demographic and clinicopathologic characteristics of the patients were recorded as numbers with percentage, mean with standard deviation and 95% CI and median with inter-quartile range (IQR). The differences between the groups were analyzed with the Chi-square test and Kruskal Wallis test respectively with a 5% level of significance [14] [15]. Cox proportional hazards model identified factors affecting survival between the two cohorts. Survival of EOC patient was defined as time from disease diagnosis to death of the patient or to the last follow-up. Kaplan-Meier survival curves with log rank test compared outcomes [16] [17]. The graph plotted between estimated survival probabilities (on Y axis) and the time past after starting follow-up (on X axis). All analyses were done using R-statistical software (Version 4.2.2). A p-value less than 0.05 was regarded as statistically significant.

3. Results

We analyzed 129 patients in our study with the overall median age of 46 (IQR: 38, 56) years. The median follow-up time was nine (IQR: 4, 26.5) months for this cohort. A total of 64 women with EOC were in the younger group (≤45 years) and 65 women were in the older age group (>45 years). The clinicopathologic characteristics of all patients are shown in **Table 1**.

Table 1. Clinicopathologic characteristics of the patients.

Characteristics	Breakdown of Factors	Age Group ≤ 45 years N = 64	Age Group > 45 years N = 65	p value
Age (years) Median (IQR)		36 years (27, 41)	56 years (50, 60)	<0.001
FIGO Stage N (%)	Stage I	20 (31.2%)	10 (15.4%)	0.167
	Stage II	3 (4.7%)	6 (9.2%)	
	Stage III	32 (50.0%)	39 (60.0%)	
	Stage IV	9 (14.1%)	10 (15.4%)	
CA125 at diagnosis N (%)	≤200	10 (26.3%)	2 (5.9%)	0.044
	>200	28 (73.7%)	32 (94.1%)	
Age of menarche (years), median (IQR)		12 (12, 13)	12 (12, 13)	0.935
Age of menopause (years), median (IQR)		41 (40, 45)	50 (45, 52)	<0.001
Menopausal n (%)		16 (25%)	64 (98.46%)	<0.001
Timing of surgery—Days from diagnosis for PDS & staging	*PDS	18 (28.1%)	20 (30.8%)	0.603
	*IDS	22 (34.4%)	26 (40.0%)	
Days from last chemo for IDS	Staging laparotomy	24 (37.5%)	19 (29.2%)	
Follow-up (months, median (IQR)		12 (6, 42)	6 (3, 18)	0.016)
Interval between diagnosis and surgery (days), median (IQR)		46.50 (28, 94.75)	52 (27, 92)	0.815
Survival N (%)	Alive	27 (43.5%)	12 (20.0%)	0.005
	Dead of Disease	35 (56.5%	48 (80%)	
Histopathology N (%)	Serous	48 (75%)	54 (83.1%)	0.021
	Mucinous	11 (17.2%)	2 (3.1%)	
	Other	5 (7.8%)	9 (13.8%)	

*PDS—primary debulking surgery; IDS—interval debulking surgery.

Thirty-one percent of patients in ≤45 years age group had stage I tumors. In contrast, the proportion of patients with stage I tumors was only 15.4% in the >45 years age group. Patients in the older age group had more advanced tumors (75% stage III and IV) than those in young age group (64% stage III and IV) which was not statistically significant (p = 0.167). Age of menopause and preoperative CA-125 level were significantly higher in the older cohort (p < 0.001 and p = 0.044 respectively). Older age group participants had reduced survival in the first six months of follow-up (p = 0.005). Serous histology was the most common histopathology in both cohorts.

All patients underwent surgery with an equivalent proportion having primary cytoreductive surgery (28% - 30%) compared to interval debulking surgery (34% - 40%). The average time delay from diagnosis to start of treatment (operation) was 46 days (younger group) and 52 days (older group). Three to six cycles chemotherapy were given prior to IDS with carboplatin and paclitaxel. Patients who underwent IDS and PDS received postoperative adjuvant chemotherapy with paclitaxel and carboplatin for serous carcinoma and gemcitabine and carboplatin for mucinous carcinoma. The total number of chemotherapy cycles varied from zero (0) to eighteen (18). A few patients did not receive the adjuvant chemotherapy as they died within a month after surgery. Two women in the younger age group died after primary debulking surgery and three women in the

older age group (two after PDS and one after IDS) with a 3% and 4.6% postoperative mortality. Postoperative complications after extensive surgery included wound infection, incisional dehiscence, sepsis, and renal failure. One patient died from a postoperative cardiac arrest.

Figure 1 compares the outcomes by age cohort. The 5-year overall survival rates (95% CI) for the younger age versus older group were 34.0% (23.0%, 50.0%), and 11.7% (5.2%, 26.1%) respectively. The difference in overall survival was significant (p = 0.021) between the two age groups (Figure 1(a)). There was a significant difference (p = 0.018) in the overall survival probability between the two groups when stratified according to the adjuvant chemotherapy (CT) (Figure 1(b)). When we consider the stage of the tumor, there were no significant differences in the overall survival between the groups (group A vs. B: stage I-II, p = 0.25; stage II-IV, p = 0.11) (Figure 1(c) and Figure 1(d)). There was a significant difference in the overall survival between the two age groups by preoperative CEA level (p = 0.003) (Figure 1(e)).

Table 2 summarizes the univariate and multivariate analysis of EOC patients who were stratified by age, FIGO stage, histological type, primary modality of treatment, preoperative CA-125 and CEA level, and adjuvant chemotherapy. By univariate analysis, except for histological subtype, all other factors such as age, FIGO stage, preoperative CA-125 and CEA level were identified as factors associated with a poorer overall survival. Adjuvant chemotherapy and staging laparotomy were identified as factors associated with a better overall survival. By multivariate analysis, stage and adjuvant chemotherapy were highly associated with overall survival. However, age was not an independent prognostic indicator for overall survival (>45 years vs. ≤45 years: hazard ratio [HR], 1.24; 95% confidence interval [CI], 0.77 to 2.00, p = 0.373). The primary modality of treatment, interval debulking or cytoreductive surgery (IDS) versus upfront primary debulking or cytoreductive surgery (PDS) showed a hazard ratio of 0.68 suggesting a trend toward better survival with neoadjuvant chemotherapy followed by surgery (95% CI, 0.40 to 1.17, p = 0.16). Similarly, an upfront staging laparotomy to obtain histopathological information but without complete resection of disease compared to primary cytoreduction did not change overall survival (HR, 0.70, 95% CI, 0.26 to 1.90, p = 0.480).

Figure 2 shows the logrank analysis adjusting by age, preoperative CA-125 level, CEA level, primary modality of treatment and adjuvant chemotherapy. With this analysis, age, CEA, and primary modality of treatment retained significance as prognostic factors for overall survival.

4. Discussion

In this study, we retrospectively analyzed clinicopathological features and the survival outcomes of 129 Bangladeshi women with Epithelial Ovarian Cancer (EOC). We demonstrated a significant lower survival for patients aged greater than 45 years compared to patients younger than or equal to age 45 years by univariate analysis. Thus, the probability of dying from ovarian cancer is higher for

the older age group. There were significantly different clinicopathological characteristics between the two age groups. Age of menopause, preoperative CA-125 level, histopathological type and outcome of disease were significantly associated with the age. Patients in the older age group had more advanced tumors (75% in stages III and IV) than those in young age group (64% in stages III and IV). It is interesting that the median age of menopause is 41 years in younger patients. But only 25% (n = 16) of younger group were in menopause. In contrast, 98% (n = 64) of older EOC patients were in menopause.

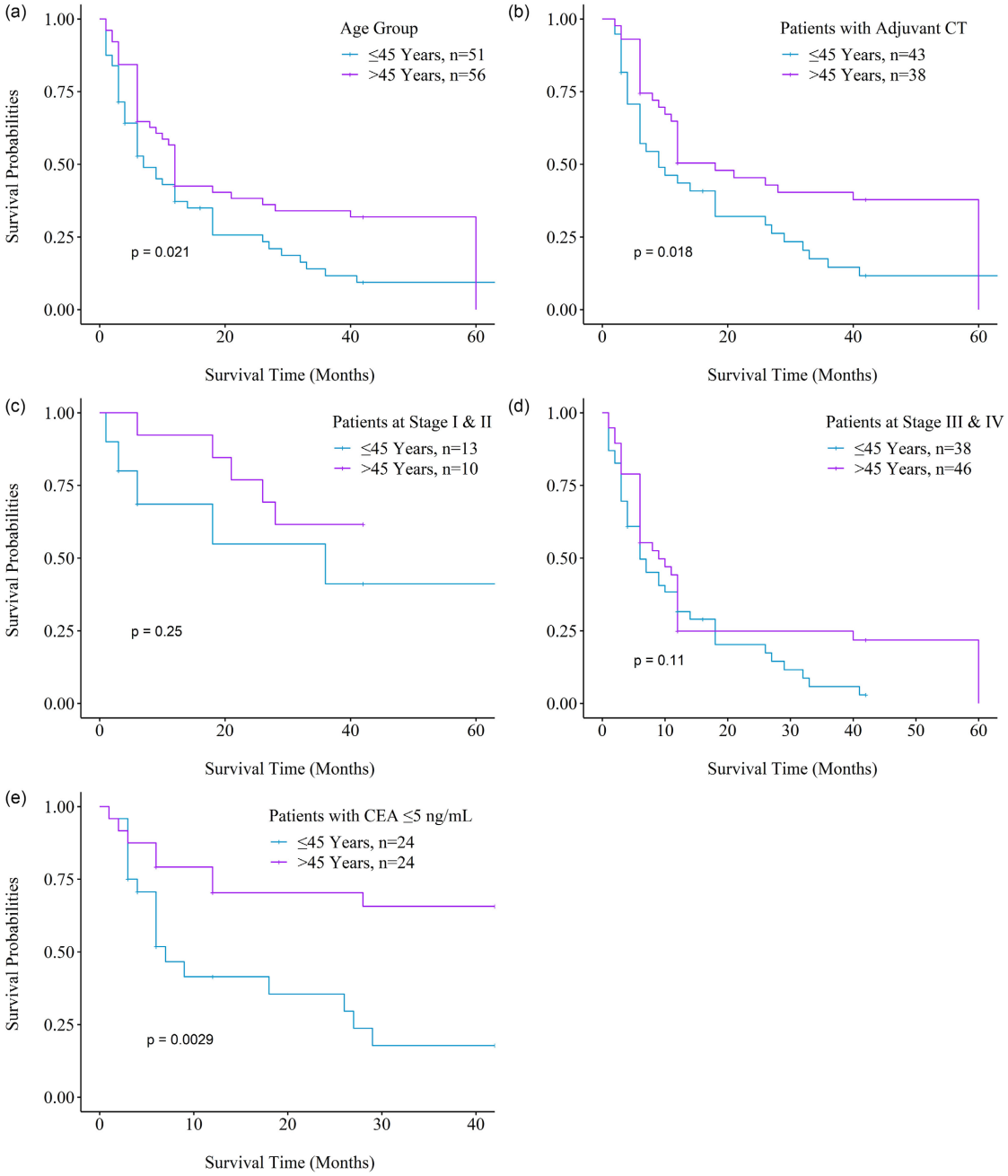

Figure 1. Kaplan-Meier estimated overall survival of patients according to the (a) Age Groups, (b) Adjuvant CT, (c) Stage I & II, (d) Stage III & IV and (e) Preoperative CEA.

Table 2. Univariate and multivariate analyses of clinicopathologic factors in relation to overall survival of patients.

Characteristics	Breakdown of Factors	Univariate Hazard Ratio (95% CI)	p value	Multivariate Hazard Ratio (95% CI)	p value
Age	≤45 Years	1	--	1	--
	>45 Years	1.64 (1.05, 2.55)	0.029	1.24 (0.77, 2.00	0.373
FIGO Stage	Stage I	1	--	1	--
	Stage II	5.55 (1.55, 19.84)	0.008	4.71 (1.30, 17.14)	0.019
	Stage III	6.45 (2.32, 17.96)	<0.001	4.98 (1.30, 18.99)	0.019
	Stage IV	13.87 (4.55, 42.27)	<0.001	10.13 (2.28, 45.02)	0.002
Histopathology	Serous	1	--		
	Mucinous	0.74 (0.34, 1.63)	0.459		
	Other	1.08 (0.54, 2.17)	0.827		
Primary modality of treatment	*PDS	1	--	1	--
	IDS	0.98 (0.61, 1.59)	0.940	0.68 (0.40, 1.17)	0.616
	Staging laparotomy	0.34 (0.18, 0.64	<0.001	0.70 (0.26, 1.90)	0.480
Preoperative CA 125	≤200 U/mL	1	--		
	>200 U/mL	2.41 (0.86, 6.75)	0.095		
Preoperative CEA	≤5 ng/mL	1	--		
	>5 ng/mL	3.62 (1.78, 7.37)	<0.001		
Adjuvant chemotherapy	No	1	--	1	--
	Yes	0.30 (0.18, 0.51)	<0.001	0.39 (0.22, 0.69)	0.001

*PDS—primary debulking surgery; IDS—interval debulking surgery.

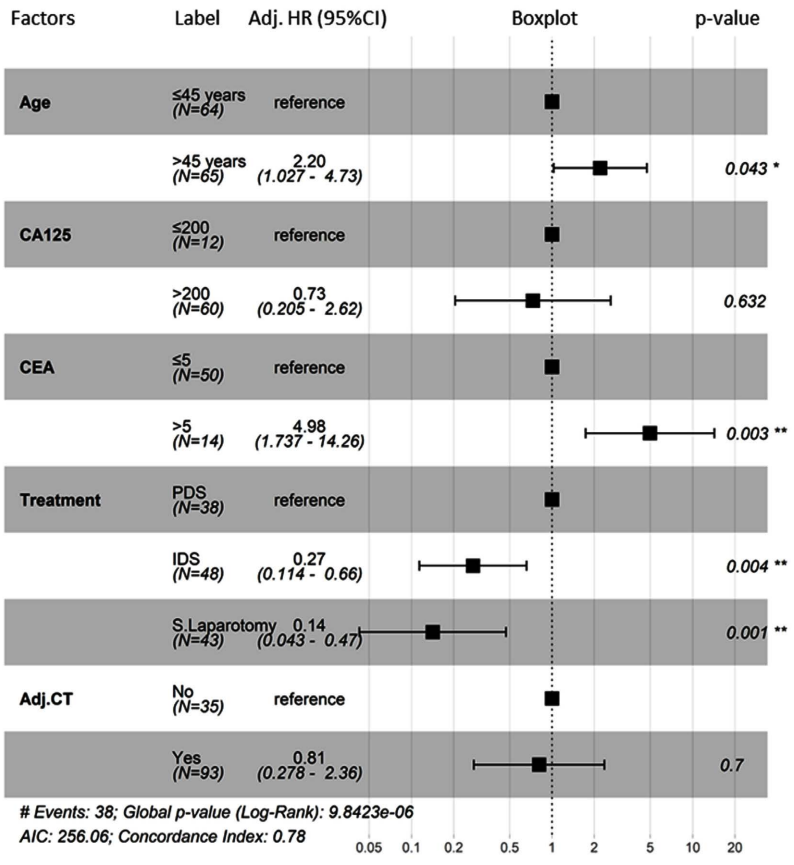

Figure 2. Multivariate analyses of clinicopathologic factors in relation to overall survival of patients.

Epithelial Ovarian cancer (EOC) has a high mortality rate. There are well established risk factors for recurrence and survival for EOC that can be separated into tumor factors, patient factors, and treatment factors. Tumor factors include characteristics of the cancers such as stage, pathologic cell type, histologic grade, and somatic genetic mutations specific to the neoplastic cells [3] [10]. Patient factors include age of diagnosis, comorbidities, germline mutations, and family history. Treatment factors include delay in diagnosis, access of healthcare and ability to pay for care, optimal cytoreductive surgery, speedy access to chemotherapy—both intravenous and intraperitoneal, access to antiangiogenetic agents and PARP inhibitors, and supportive care such as access to antibiotics, nutrition, and blood products. Most reported studies are from the United States and Europe.

In a multivariate analysis of 65 women with stage III and IV EOC, adjuvant chemotherapy (HR = 0.046; p-value = 0.000492), suboptimal cytoreduction (HR = 0.346; p-value = 0.021219), and postoperative complications (p-value = 0.001389) were independent prognostic factors for overall survival [18]. Optimal surgical cytoreduction (R less than 1 cm residual disease) whether as primary upfront surgery or at interval surgery after neoadjuvant chemotherapy has been well established as a leading prognostic factor for improved survival [19]. In a retrospective analysis of 207 patients with advanced ovarian cancer, complete cytoreduction to no visible disease (R = 0 mm) led to a significantly better survival than optimal cytoreduction and this was most likely accomplished with bowel resection [20]. The use of neoadjuvant chemotherapy followed by interval cytoreductive surgery is a useful treatment strategy for advanced bulky disease [13] [21]. A recent prospective randomized trial of upfront surgery versus interval surgery in 171 patients with advanced EOC confirmed equivalent survival with a median progression free survival and overall survival of 15 and 41 months versus 14 and 43 months in the primary cytoreductive surgery and neoadjuvant chemotherapy arms respectively [22]. However, in many resource-limited environments, six cycles of chemotherapy are routinely given upfront prior to referral to surgery because a limited number of trained gynecologic oncologists and a long queue for surgery. There has been concern that prolonged primary chemotherapy prior to surgery may lead to an increase in platinum resistant disease [23]. In a retrospective analysis of 199 women who received neoadjuvant chemotherapy, five or more cycles of neoadjuvant chemotherapy were associated with a worse progression-free survival (HR 2.2; p-value < 0.001) even after adjustment for BRCA status and complete cytoreductive surgery [24].

In this study, we investigated the clinical features of Bangladeshi EOC patients stratified into older and younger age groups. All 129 patients underwent aggressive cytoreductive surgery either as primary or interval surgeries. EOC is a lethal malignant condition in women, and it is commonly diagnosed in postmenopausal women which is also reflected in our analysis [3]. The FIGO staging is a significant prognostic factor for EOC patients [3] [25] [26]. Our results confirm

that in a South Asian population, advanced FIGO stage decreased the overall survival in the older age group [27].

We identified age as an independent prognostic factor among our study participants by univariate analysis but not by multivariate analysis. In this present study, univariate analysis disclosed that younger age was a significant prognostic factor for EOC cases, but this significance did not stand for multivariate analysis. This suggests that the results may be related to the distribution of the tumor stage. Some previous studies compared the prognosis between younger and older patients with a cut-off age of 40 years [3]. However, we consider the cut-off age of 45 years, as the median age of our study population was 46 years. On the other hand, Trillsch *et al.* considered the cut-off age as 70 years and that was a study of EOC patients in Western countries [28]. A study in a French population revealed a significant association between age and OS in EOC patients [29]. Another study among a US population reported that relatively younger age patients independently led to a favorable prognosis and was an independent prognostic factor when considering the analysis of EOC patients with stage III-IV [9] [30]. In Japan, age (<40 years) of the patients with EOC was not an independent prognostic factor for OS [3]. Seeing the differences in geographical locations and genetic background, most previous studies suggested that age can be an independent prognostic factor among EOC cases, and this was consistent with our present findings that younger age EOC patients were correlated with improved prognosis which may be partly related to a larger proportion diagnosed at earlier stages. At this writing, there are few reports from Asia.

By multivariate analysis of clinicopathologic factors in relation to overall survival of patients, except FIGO stage adjusting by age, preoperative CA-125 level, CEA level, primary modality of treatment and adjuvant CT, age, CEA, and primary modality of treatment retained significance as prognostic factors for overall survival. An important limitation of this study is its retrospective nature. Prospective study is needed to identify more clinicopathological features and the risk factors. The other limitations of this study included heterogeneous treatment protocols with different chemotherapy regimens and types of surgery and a lack of BRCA status for our patients [31]. While aggressive cytoreductive surgery with the resection of disease to no residual or less than 1 cm residual disease is associated with better survival, we were not able to retrieve that information for this study due to the lack of electronic medical records and limitations in how operative notes are written in Bangladesh [32]. All data were retrospective and no exact information was recorded in operation notes regarding optimal surgery. During our enrollment period, BRCA testing was not routinely done in the NICRH. At that time, BRCA testing was expensive, time-consuming and only available in few private centers where collected sample from patients were sent to India for testing. In this current study, all our patients belonged to poor to middle-income families and could not afford BRCA testing. Further studies with larger populations of EOC in other Asian countries including Bangladesh are needed to understand the genetic associations with epithelial ovarian cancers.

Author Contribution Section

Farhana Haque: conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing original draft, writing review & editing, visualization, project administration, funding acquisition. Shahana Pervin: conceptualization, methodology, investigation, writing review & editing, supervision, funding acquisition. Annekathryn Goodman: writing, data analysis.

Highlights

Significantly low survival for patients at the age of older age group than the younger age group.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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