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GYNECOLOGIC ONCOLOGY

The preoperative albumin level is an independent prognostic factor for optimally debulked epithelial ovarian cancer

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Abstract
Purpose A low albumin level has been reported to be a prognostic factor for various cancers. The aim of this study was to determine the association between preoperative serum albumin level and survival in patients with epithelial ovarian cancer (EOC).
Methods Records of 337 patients with EOC that underwent optimal cytoreductive surgery were retrospectively reviewed. Threshold albumin level was planned as 32.5 g L^{-1} due to the statistical analyses.
Results Mean overall survival was 51.5 months. Area under the ROC curve was found statistically significant for the discriminative role of albumin for survival outcome (AUC = 0.857, 95% CI 0.813–0.90, $P < 0.001$). The best cut-off point for albumin was determined as 32.5 g L^{-1}. The sensitivity rate, specificity rate, positive and negative predictive values, and accuracy rate for this cut-off level were found 67.2, 91.2, 81.2, 83.1, and 82.5%, respectively. Preoperative hypoalbuminemia was noted in 101 (30.0%) of the patients, of which 6.2% had an albumin level <25 g L^{-1}. The albumin level was independently and significantly associated with overall survival (HR 2.6; 95% CI 2.1–3.1; $P < 0.001$). Subgroup analysis showed that patients with an albumin level <32.5 and ≥32.5 g L^{-1} had mean estimated overall survival of 40.6 and 96.0 months, respectively. Age, stage, and presence of ascites were the other independent significant factors.
Conclusions The preoperative albumin level is an independent prognostic factor for overall survival in optimally debulked EOC patients. Further investigations about preoperative albumin level in prognostic models will contribute to the literature.

Keywords Optimal debulking · Ovarian cancer · Overall survival · Preoperative albumin

Introduction

Ovarian cancer accounts for the 3.6% of all cancers, with 239,000 new cases and 4.3% of all cancer-related deaths in females annually [1]. Epithelial ovarian cancer (EOC) is the most common histological type of ovarian cancer and the initial treatment includes surgery followed by chemotherapy. It is well known that the surgical outcome directly affects survival [2–5]. The majority of EOC patients are diagnosed at an advanced stage due to an asymptomatic disease process with non-specific signs and commonly require aggressive surgical treatment.

Advanced-stage disease is frequently associated with ascites, nutritional deficit, weight loss, and poor patient performance. Various parameters, including hemoglobin, total protein, albumin, and transferrin, are used to evaluate nutritional status in patients with gynecological cancers [6]. Albumin is the most abundant plasma protein. It is synthesized in the liver, but is not stored. The rate of albumin synthesis is associated with nutritional and disease states

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[7], and the albumin level is an objective parameter used to measure malnutrition.

Ovarian cancer is the most common one associated with hypoalbuminemia among gynecological cancers. There are multiple mechanisms to be accused of hypoalbuminemia in ovarian cancer such as: most of the patients are diagnosed at advanced stage that causes decreased motility in the gastrointestinal tract, resulting a worse digestion, reduced appetite, and malnutrition in various levels; ascites causes loss of proteins in the intravascular space; the tumor burden causes a cytokine-related systemic effect resulting a negative nitrogen balance.

Hypoalbuminemia is a risk factor for poor perioperative results in gynecological cancer patients [8–10]. Moreover, hypoalbuminemia is associated with survival in patients with such cancers as glioblastoma multiforme [11], gastric cancer [12], breast cancer [13], ovarian cancer [9, 14], endometrial cancer [15], head and neck cancer [16], and non-small cell lung cancer [17]. Based on these findings, the present study aimed to determine the association between the preoperative serum albumin level and survival in patients with EOC that underwent optimal cytoreductive surgery.

Materials and methods

This is a retrospective non-randomized study including a single center experience. EOC patients that underwent primary cytoreductive surgery were retrospectively evaluated. Data were obtained from hospital records, and patients that underwent surgery between 2007 and 2014 were included. Optimally debulked patients were included in the study to minimize the heterogeneity due to the differences in residual tumor volume. Optimal debulking was defined as cytoreductive surgery with residual tumor volume <1 cm [18]. Exclusion criteria were non-optimal surgery (residual tumor volume ≥1 cm), a history of neoadjuvant chemotherapy, incomplete follow-up data, and any disorder affecting the albumin level (such as liver deficiency and nephrotic syndrome). All patients underwent standard surgery, including hysterectomy, bilateral salpingo-oophorectomy, bilateral para-aortic and pelvic lymph node dissection, omentectomy, appendectomy, and peritoneal tumor resection, and extended surgery in cases of metastatic disease. Paclitaxel and platinum-based adjuvant chemotherapy were planned postoperatively [19]. The study included 337 of 401 patients that met the inclusion criteria. Distribution of excluded patients was as follows: residual tumor volume ≥1 cm and interval debulking 51 patients, neoadjuvant chemotherapy for 13 patients. All of these patients had an ASA score of ≥3.

The FIGO (International Federation of Gynecologists and Obstetricians) system was used for disease staging. Disease stage was classified as early (stage I and II) and advanced (stage III and IV). Disease grade was classified as low (G1 and 2) and high (G3 and clear cell).

A surgical complexity score (SCS) was also used for definition of extension of procedures as reported previously [20].

Data were analyzed using SPSS for Windows v.15.0 (SPSS, Inc., Chicago, IL, USA). Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Kaplan–Meier and Cox regression analyses were used to analyze survival. Logistic regression analysis was used to evaluate independent samples affecting albumin level. A receiver-operating characteristic (ROC) curve was used to assess the discriminative role of the albumin level and Ca125 level between alive and dead patients. Area under a curve was found significant for both variables. The point at which the sum of specificity and sensitivity reached the maximum was taken as the best cut-off point. Cut-off point for albumin and Ca125 was determined as 32.5 g L^{-1} and 248.6 IU, respectively. The patients were divided into three subgroups according to the albumin level: <25, 25–34, and ≥35 g L^{-1}. The level of statistical significance was set at $P < 0.05$.

Results

Study included 337 patients with a mean age of 53.7 ± 11.9 years (range 21–87 years) and 68.8% of the patients were aged <60 years. Mean overall survival was 51.5 ± 24.0 months (range 4–112 months). General patient characteristics are shown in Table 1. The incidence of serous histology, G3 disease, and advanced-stage disease was 73.3, 56.7, and 70.3%, respectively. In all, 237 patients underwent standard surgery and 100 patients underwent extended surgery. Surgical characteristics are summarized in Table 2.

Area under the ROC curve was found statistically significantly for the discriminative role of albumin for survival outcome (AUC = 0.857, 95% CI 0.813–0.90, $P < 0.001$) (Fig. 1). The best cut-off point for albumin level predicting the survival outcome was determined as 32.5 g L^{-1}. The sensitivity rate, specificity rate, and positive and negative predictive values were found 67.2, 91.2, 81.2, and 83.1%, respectively. The diagnostic accuracy rate was 82.5% at this point.

Preoperative hypoalbuminemia was noted in 101 (30.0%) of the patients and 6.2% of the patients had an albumin level <25 g L^{-1}. According to multivariate analysis, advanced-stage disease (HR 2.4; 95% CI 1.5–3.8; $P < 0.001$) and ascites (HR 1.4; 95% CI 1.01–1.8; $P = 0.04$) were independent factors significantly associated with the albumin level. Factors associated with the albumin level based on univariate analysis are shown in Table 3.

Table 1 General properties of patients

	N	%
Age (mean–range)	53.7 (21–87)	
FIGO stage		
Early (stage 1–2)	100	29.7
Advanced (stage 3–4)	237	70.3
Histology		
Serous	247	73.3
Mucinous	16	4.7
Endometrioid	24	7.1
Clear Cell	32	9.5
Others	18	5.3
Grade		
Low (grade 1–2)	114	33.8
High (grade 3—clear cell)	223	66.2
Level of serum albumin (g L^{-1})		
<25	21	6.2
25–34	141	41.8
>35	175	51.9
Status		
Alive	215	63.8
Dead	122	36.2

FIGO International Federation of Gynecologists and Obstetricians

Table 2 Surgical properties of patients

	N	%
Ascites		
<500 cc	153	45.4
≥500 cc	184	54.6
Patients underwent extended surgery	100	29.7
Number of performed extended procedures	144	
Extended approaches		
Splenectomy	44	13.6
Intestinal resection	22	6.5
Diaphragma stripping/resection	18	5.3
Peritonectomy	55	16.3
Cholecystectomy	6	1.8
Postoperative complication rate	61	18.1
Intensive care unit need	32	9.5
SCS (surgical complexicity score)		
<3	9	2.7
4–7	274	81.3
>8	54	16.0

Prognostic factors were evaluated via multivariate and univariate analyses, separately. Prognostic factors according to univariate analysis are shown in Table 4. Multivariate analysis of age, histology, disease grade, LVI, para-aortic lymph node involvement (PaLNI), lymph node involvement

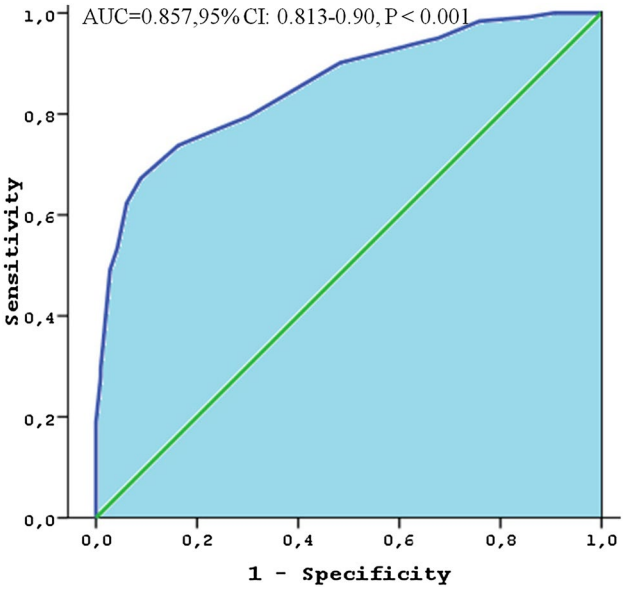

Fig. 1 Graphical presentation of ROC curve analyses for albumin level

Table 3 Factors related with albumin level—Cross-Tabs, Chi-square analyses

	Albumin <32.5 g L^{-1}		Albumin ≥32.5 g L^{-1}		
	N	%	N	%	*p* value
Age (years)					
<60	102	63.0	130	74.3	0.17
≥60	60	37.0	45	25.7	
Ascites (cc)					
<500	48	29.6	105	60.0	<0.001
≥500	114	70.4	70	40.0	
Histology					
Serous	135	83.3	112	64.0	<0.001
Others	27	16.7	63	36.0	
Grade					
Low	48	29.6	66	37.7	0.07
High	114	70.4	109	62.3	
LNI					
Present	100	61.7	62	35.4	<0.001
Absent	62	38.3	113	64.6	
FIGO stage					
Early	22	13.6	78	44.6	<0.001
Advanced	140	86.4	97	55.4	
Chronical disease					
Present	65	40.1	68	38.9	0.45
Absent	97	59.9	107	61.1	

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Table 4 Univariate and multivariate analyses of prognostic factors for overall survival—Kaplan–Meier analyses and cox regression analyses

	Univariate survival analysis				Multivariate survival analysis			
	Mean survival (months-estimate)	95% CI		*P* value	HR	95% CI		*P* value
Age (years)								
<60	83.4	78.1	88.7	0.002	1			0.03
≥60	67.5	59.4	75.5		1.2	1.01	1.5	
FIGO stage								
Early	103.0	98.4	107.6	<0.001	1			0.006
Advanced	68.2	62.6	83.7		1.7	1.2	2.6	
Histology								
Serous	72.3	66.9	77.7	<0.001				0.32
Others	93.9	86.5	101.3					
Grade								
Low	81.3	73.4	89.3	0.164				0.76
High	77.2	71.6	82.8					
LVI								
Present	69.1	63.4	74.9	<0.001				0.33
Absent	90.7	84.3	97.2					
PaLNI								
Present	59.0	50.8	67.3	<0.001				0.21
Absent	86.1	81.0	91.2					
LNI								
Present	63.1	56.8	69.4	<0.001				
Absent	92.2	86.7	97.8					
Ca125 level (IU)								
<248.6	93.6	87.7	99.4	<0.001				
≥248.6	65.2	59.2	71.1					
Ascites (cc)								
<500	95.1	89.7	100.5	<0.001	1			0.02
≥500	62.5	56.3	68.7		1.3	1.05	1.7	
Preoperative albumin level (g L^{-1})								
<32.5	40.6	34.5	46.8	<0.001	2.6	2.1	3.1	<0.001
≥32.5	96.0	91.6	100.5		1			

FIGO International Federation of Gynecologists and Obstetricians

(LNI), disease stage, the Ca125 level, ascites, and the preoperative albumin level showed that the albumin level was independently and significantly associated with overall survival (HR 2.6; 95% CI 2.1–3.1; $P < 0.001$). Moreover, in multivariate analysis of patients with advanced-stage disease of age, histology, disease grade, LVI, para-aortic lymph node involvement (PaLNI), lymph node involvement (LNI), the Ca125 level, ascites, and the preoperative albumin level showed that the albumin level was independently and significantly associated with overall survival (HR 2.52; 95% CI 2.06–3.08; $P < 0.001$). The other significant independent prognostic factors were age, disease stage, and presence of ascites (Table 4). In univariate analyses, patients with an albumin level <32.5 and ≥32.5 g L^{-1} had mean estimated overall survival of 40.6 and 96.0 months, respectively ($P < 0.001$). In addition, subgroup analysis according to the albumin level (<25, 25–34, and ≥35 g L^{-1}) showed that mean estimated overall survival was 19.6, 62.2, and 79.1 months, respectively.

Majority of patients had intermediate SCS level. The surgical properties of patients were summarized in Table 2. The most frequent postoperative complications were ileus (20 patients, 6.0%), wound infection (18 patients, 5.4%), and pleural effusion (17 patients, 5.1%). Thirty-two patients (9.5%) needed postoperative intensive care. Moreover, the preoperative albumin level was not associated with the postoperative complication rate or the requirement of intensive care, whereas the presence of ascites was associated with both ($P < 0.001$ for both) and age was associated with the requirement of intensive care ($P = 0.038$), according to multivariate analysis.

Discussion

The albumin synthesis and degradation rates and its distribution through the body are determinants of the serum albumin level [7]. Serum albumin level is one of the laboratory measurements that can be used for nutritional status of patients [21, 22]. Normal range of albumin is 3.5–5 g/dL in adults and levels <3.5 g/dL are defined as hypoalbuminemia [23]. Ovarian cancer-related hypoalbuminemia is a result of a decrease in the synthesis of and an increase in leakage of albumin to the extravascular space with ascites. There is a lack of consensus concerning the albumin cut-off level [14, 24].

Cancer patients frequently have lower albumin levels especially in advanced stages. Multiple mechanisms may result in hypoalbuminemia in these patients. Malnutrition, low appetite, and weight loss are common problems. This results in low intake of aminoacids and a negative nitrogen balance and degradation in albumin synthesis. Another factor that decreases the albumin synthesis is inflammation [25]. Increased inflammatory response with the production of cytokines such as interleukin-6 and tumor necrosis factor is detected in cancer patients with lung cancer and various gastrointestinal system cancers [26–28]. EOC has an asymptomatic course and the majority of patients have advanced-stage disease at the time of presentation. Advanced-stage disease is usually accompanied by high tumor burden, ascites, weight loss or cachexia, and varying degrees of malnutrition. It was reported that 24% of patients with gynecological cancers are malnourished and those with ovarian cancer have the highest rate of malnutrition (67%) [21].

There is an association between preoperative hypoalbuminemia, and postoperative morbidity and mortality of gynecological and non-gynecological approaches [8, 9, 24, 29, 30]. Moreover, an albumin fall occurs after surgery [31]. In addition to the short-term effects mentioned above, the preoperative albumin level is associated with survival in various cancers. Moreover, a study that included 337 endometrial cancer patients showed there was an association between the pretreatment serum albumin level, and disease-free survival ($P = 0.02$) and progression-free survival ($P < 0.001$) [15]. Ovarian cancer is the most common gynecological cancer that occurs concomitantly with hypoalbuminemia. A review about pretreatment albumin levels including 29 studies about various cancers concludes that pretreatment of serum albumin levels provide useful prognostic significance in cancer [32]. There are several studies in the literature evaluating the prognostic value of albumin in ovarian cancer. Asher et al. reported that there is an association between a low albumin level and poor survival in ovarian cancer patients [14]. They also reported that there is an inverse correlation between a low albumin level and median survival. Gupta et al. investigated the role of albumin level with a cutoff of 3.6 g/dL and reported a relative risk of 0.39 for every one g/dL increase ($P < 0.001$) [33]. A recent study that included 604 EOC patients observed a strong correlation between a low albumin level and median overall survival ($P = 0.002$, 24 vs. 83 months) [8]. An albumin level of ≥3.7 g/dL was found in association with 40% reduction in mortality risk in over than 80 years ovarian and primary peritoneal cancer patients [34]. Also there are published data about the importance of albumin level using in prognostic models for ovarian cancer [35–38].

Albumin is the most abundant plasma protein and has a wide range in EOC patients. Advanced-stage patients who were subjected to more aggressive surgical approaches need albumin replacement. Recent studies emphasize the importance of preoperative albumin level in short-term and long-term results. Prospective studies regarding the albumin replacement preoperatively and postoperatively may open new horizons in management of these patients. The use of fresh frozen plasma and total parenteral nutrition, or high-protein diet before and after surgery may be discussed with albumin levels.

The present findings are in agreement with those of earlier studies on the relationship between the preoperative albumin level and survival in patients with various cancers, including ovarian cancer. Optimally debulked patients were included in the study to minimize heterogeneity. Exploration of intraoperative data, standard surgical and medical management of single center, and substantial number of patients for single center are considered as strengths of the study. On the other hand, lack of a clearly defined optimal albumin level and cut-off level for hypoalbuminemia, retrospective design, and lack of power analysis are considered limitations of the present study retrospective.

Conclusion

The present study investigated the relationship between the preoperative albumin level and overall survival in EOC patients, and observed an association between the serum albumin level and overall survival. In addition, disease stage and the Ca125 level were independently associated with overall survival. Moreover, there was not an association between the albumin level and perioperative outcome in the present study, in contrast to earlier studies. Based on the present findings, we think that additional prospective studies on the effect of the preoperative albumin level on survival in patients with gynecological cancers are warranted. Furthermore, the albumin level might be used for preoperative evaluation of patients and can be used in risk prediction models.

Author contributions EG: project development, data collection and management, data analysis, manuscript writing, and editing. İAK: project development, data collection, manuscript writing, and literature search. NH: data analysis and editing. ÖÖA: project development and data management investigation. PD: manuscript writing and editing, and supervision. AA: project development, data management, data analysis, manuscript editing, and supervision.

Compliance with ethical standards

Ethics statement Ethical approval for the present study was not required, as it was retrospectively performed.

Conflict of interest The authors declare there are no conflicts of interest—financial or otherwise—related to the material presented herein.

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