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ORIGINAL PAPER

Preoperative serum albumin is an independent prognostic predictor of survival in ovarian cancer

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Abstract Ovarian cancer is associated with high mortality due to asymptomatic nature of the disease and advance stage at presentation. In advanced stages, it is associated with cachexia and ascites leading to malnutrition. Nutritional status of a patient with cancer has been well known to be associated with survival and can be assessed by level of albumin in blood. Therefore, in this study, we sought to determine preoperative serum albumin as prognostic predictor of survival in patients with ovarian cancer. Preoperative serum albumin was determined in 235 patients undergoing surgery for ovarian cancer at Royal Derby Hospital. The prognostic predictive value of serum albumin, along with other prognostic markers was then analysed using univariate and multivariate analyses. Low serum albumin was associated with poor survival ($P < 0.001$) in patients with ovarian cancer. There was an inverse correlation between serum albumin levels and survival with lower levels having poor survival. Patients with serum albumin levels of <25 g/l had a median survival of 4.8 months (95% CI 0–13.1 months), whilst levels >35 g/l were associated with median survival of 43.2 months (95% CI 11.6–20.9). Serum albumin ($P < 0.001$) retained its significance as an independent predictor of poor survival on Cox's multivariate regression analysis along with Age ($P < 0.001$) and FIGO stage ($P < 0.001$). Serum albumin can be used as an independent prognostic predictor of survival in patients with ovarian cancer.

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Background

There are more than 225,000 cases of ovarian cancer diagnosed worldwide, accounting for almost 4% of all cancer diagnosed in women [1]. It is estimated that there will be almost 21,880 new cases and 13,850 deaths due to ovarian cancer in the United states in 2010 [2].Ovarian cancer accounts for more deaths that all other gynaecological cancer put together, this is partly due to presentation at late stage and lack of specific symptoms [3]. Advanced stage disease is often associated with omental cake, ascites resulting in poor nutritional status [4]. Malnutrition is associated with increased post-operative complications [5], poor clinical outcome [6] and death [7].

Various prognostic markers such as prognostic nutritional indices, serum albumin, total protein, transferrin, haemoglobin and anthropometric measurements have been used to assess nutritional status in gynaecological cancer patients. Out of these, serum albumin as an objective parameter often used to measure long-standing malnutrition [4].

Albumin is produced by the liver and almost 60% is present in the extravascular space. It helps to maintain intravascular oncotic pressure, facilitate transport of substances and acts as a free radical scavenger [8]. Malignant disease has been shown to be associated with low albumin due to inhibitory effect on its synthesis from liver [9] and sequestration in ascites or pleural effusion.

Albumin has been shown to be a prognostic marker in colorectal cancer [10], glioblastoma multiforme [11], gastric cancer [12] and breast cancer [13]. In this study, we

have investigated the role of serum albumin as an independent prognostic predictor of survival in patients with ovarian cancer.

Methods

Retrospective data were collected for patients undergoing surgery for ovarian cancer at Derby City General Hospital from 1988 to 1998. The patients were treated initially with total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy. All the patients with stage Ic to IV disease received chemotherapy following surgery. The patients were followed up 3 months for first 2 years and 6 months thereafter for a period of 5 years. At each visit, the patients were assessed by both clinical and ultrasound examination with CA 125 evaluation to detect recurrence.

Clinico-pathological variables recorded included pre-operative serum albumin, age, FIGO stage, tumour grade, extent of cytoreduction, histological subtype, details of adjuvant treatment and disease specific survival (DSS). DSS was calculated from operation date to 31 December 2005, when remaining survivors were censored. The database was audited to ensure its validity. Patients who had received prior chemotherapy were excluded from the study.

Statistical analysis

All data were analysed using SPSS version 7 (SPSS Inc, Chicago, IL). Continuous data were analysed using median, interquartile range and 95% confidence interval (CI). Categorical data were compared using chi square or Fisher exact test. Survival variation between groups was analysed using Kaplan–Meier curve using log rank test to estimate sizes of differences in survival. Multivariate analysis was done using Cox's proportional hazards model to determine relative risk and independent significance of individual factors. A P value ≤ 0.05 was considered to be statistically significant.

Results

A total of 235 patients were identified during the study period. The median age of patient was 62 years with a median survival of 24.5 months. Almost 60% of the patients had stage 3 and 4 whilst 58% had optimal debulking surgery (Table 1). Patients with serum albumin level of <25 g/l had a median survival of 4.8 months, 25–35 g/l had a median survival of 15.2 months and in those with >35 g/l, the median survival was 43.2 months (Table 2; Fig. 1).

Table 1 Patients characteristics

Number of patients	235
Median age years (IQR)	62 (24–90)
Overall median survival months (IQR)	24.5 (0.3–191.1)
Stage	*n* (%)
1	55 (23.4)
2	28 (11.9)
3	107 (45.5)
4	34 (14.5)
Missing	11 (4.7)
Residual disease	*n* (%)
No	137 (58.3)
Yes	79 (33.6)
Missing	19 (8.1)
Grade	*n* (%)
1	23 (9.7)
2	84 (35.6)
3	77 (32.6)
Missing	52 (22)
Chemotherapy	*n* (%)
Yes	170 (72.3)
No	58 (24.7)
Missing	7 (3)
Histological type	*n* (%)
Serous	117 (49.6)
Mucinous	35 (14.8)
Endometroid	15 (6.4)
Clear cell	1 (0.4)
Mixed mullerian	1 (0.4)
Undifferentiated	66 (28)
Missing	1 (0.4)
Serum albumin (g/l)	*n* (%)
<25	25 (10.6)
25–35	93 (39.6)
>35	51 (27.7)
Missing	66 (25.1)

On univariate analysis, variables including age at diagnosis, FIGO stage, grade, residual disease and serum albumin were associated with significantly poor survival whilst CA125, chemotherapy and histological were not (Table 3).

Multivariate Cox regression analysis was then performed on the variables that were associated with poor survival on univariate analysis. Age at diagnosis, FIGO stage and serum albumin retained their significance whilst residual disease and grade did not (Table 4).

Further analysis was done by comparing the three groups based on serum albumin levels (<25, 25–35 and

Table 2 Median survival based on different levels of preoperative serum albumin

Serum albumin (g/l)	Median survival months (IQR)
<25	4.8 (0–13.1)
25–35	15.2 (12.3–18.0)
>35	43.2 (29.3–57.0)

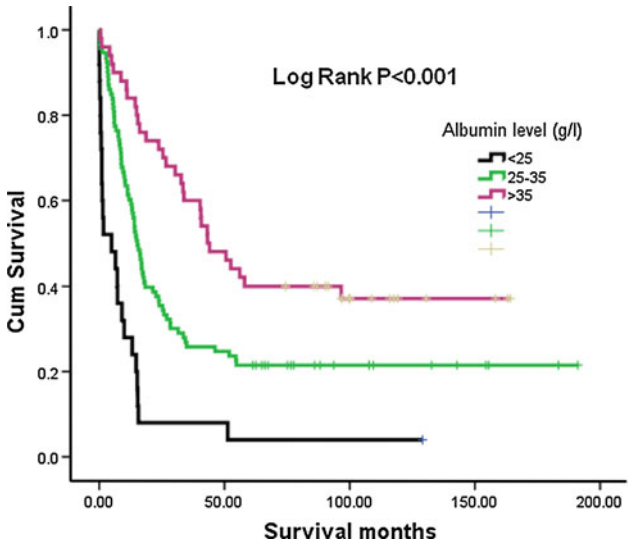

Fig. 1 Kaplan–Meier survival curves for overall survival in patients with ovarian cancer showing progressively poor survival with reducing level of serum albumin

>35 g/l) to other prognostic indicators of ovarian cancer. This demonstrated no difference in the proportion of patients receiving chemotherapy ($P = 0.06$) and CA 125 level ($P = 0.23$). Furthermore, serum albumin did not show any significant association with residual disease but was associated with FIGO stage, grade and histological type of the tumour (Table 5).

Discussion

Ovarian cancer patients are more likely to present with poor nutritional status and cachexia due to the metabolic effects of tumour mass, ascites and small bowel obstruction [14]. Malnutrition leads to reduced muscle mass and subsequently affecting the functional status of the individual. Moreover, malnourished patients have defective scarring mechanisms leading to increased post-operative wound dehiscence and infections. In these patients, the tumour is also resistant to the effect of chemotherapy resulting in poor overall survival [15].

Table 3 Analysis of survival based on prognostic markers as single variable

Variable	Hazard ratio (95% CI)	*P* value
Age	1.02 (1.01–1.03)	<0.001
Stage		
1	1	
2	2.24 (1.20–4.17)	0.011
3	3.58 (2.21–5.78)	<0.001
4	7.32 (4.16–12.87)	<0.001
Residual disease		
No	1	
Yes	2.80 (2.02–3.88)	<0.001
Grade		
1	1	
2	2.28 (1.133–4.623)	0.021
3	3.18 (1.57–6.42)	0.001
Chemotherapy		
Yes	1	
No	0.691 (0.47–1.016)	0.060
CA 125		
<35	1	
>35	1.53 (0.996–2.361)	0.06
Histological subtype		
Serous	1	
Mucinous	1.01 (0.627–1.611)	0.984
Endometroid	0.65 (0.315–1.351)	0.250
Clear cell	0.01 (0–4.70)	0.961
Mixed mullerian	1.03 (0.144–7.442)	0.973
Undifferentiated	1.63 (1.153–2.305)	0.006
Serum albumin (g/l)		
<25	1	
25–35	0.36 (0.226–0.577)	<0.001
>35	0.18 (0.109–0.327)	<0.001

There have been various parameters used to measure the nutritional status of the patients with gynaecological cancer with varied results. They include anthropometric measurements (weight loss, body mass index (BMI), triple skin fold thickness and arm circumference), biochemical (serum prealbumin, albumin, transferrin, haemoglobin, and vitamins) and immunological (skin sensitivity tests) measurements [16].

Various prognostic scoring systems such as prognostic nutritional index (PNI) [17], prognostic and nutritional inflammatory index [18] and patient-generated subjective global assessment (PG-SGA) [19], consisting of combination of different prognostic nutritional markers have also been used to the state of nutrition in critically ill and cancer patients. Of the above markers, PG-SGA, serum albumin and skin fold thickness have been shown to be accurate

Table 4 Cox proportional hazards model of various markers for survival in ovarian cancer patients

Variable	Hazard ratio (95% CI)	*P* value
Age at diagnosis	1.03 (1.013–1.057)	0.002
Stage		
1	1	
2	2.82 (0.988–8.059)	0.053
3	2.57 (1.904–6.034)	0.03
4	5.27 (2.072–13.447)	<0.001
Residual disease		
No	1	
Yes	1.31 (0.808–2.123)	0.274
Grade		
1	1	
2	1.13 (0.487–2.637)	0.771
3	1.01 (0.443–2.337)	0.968
Serum albumin (g/l)		
<25	1	
25–35	0.36 (0.208–0.639)	<0.001
>35	0.27 (0.140–0.550)	<0.001

Table 5 Prognostic markers for ovarian cancer stratified according to serum albumin levels (g/dl) (Fisher exact test)

Variable	Number of patients stratified by serum albumin level (g/l)			*P* value
	<25	25–35	>35	
Stage				
1	00	11	14	<0.001
2	02	07	07	
3	13	50	24	
4	10	19	02	
Residual disease				
No	12	43	29	0.08
Yes	13	42	14	
Grade				
1	01	05	07	0.003
2	06	32	20	
3	14	34	13	
CA 125				
<35 IU/ml	05	11	13	0.23
>35 IU/ml	14	60	30	
Chemotherapy				
Yes	87	83		0.06
No	38	20		
Histological type				
Serous	12	41	30	0.01
Mucinous	02	11	09	
Endometroid	00	09	04	
Clear cell	01	00	00	
Undifferentiated	10	32	08	

in predicting malnutrition and subsequent survival in gynaecological cancer patients [16]. We therefore used preoperative serum albumin as predictor of survival in patients with ovarian cancer.

In our cohort, serum albumin levels of <25 g/l associated with median survival of 4.8 months compared to 43.2 months in patients with serum albumin of >35 g/l with clear separation of survival curves. This correlation of poor survival with decreasing levels of serum albumin has also been demonstrated by Parker et al. [20]. They have also shown that serum CA125 in addition to albumin is also an independent prognostic predictor of survival in patients with ovarian cancer. In our study, there was no correlation of CA125, chemotherapy and histology with survival.

On Cox regression model of multivariate analysis, serum albumin retained its capability as an independent prognostic marker for poor survival in patients with ovarian cancer along with age and FIGO stage. The presence residual disease after surgery is a well-known independent prognostic marker for survival in patients with ovarian cancer [21], but in our study the presence of residual disease lost its significance as poor prognostic marker on multivariate analysis.

Further stratification of various variables with respect to serum albumin, showed that there was no difference in patients receiving chemotherapy, presence of residual tumour and CA125 level although there was a significant association of serum albumin with stage, grade and type of tumour. This indicates the low albumin is associated with aggressive disease and is associated with poor survival.

The levels of serum albumin can also be affected by other associated conditions such as liver disease, uraemia, hypothyroidism, alcohol abuse, corticosteroids and trauma [22]. Moreover, albumin has a large body pool and a half life of 20 days and once the pool is depleted, it takes typically 14 days to return to normal on adequate nutrient supplementation [23].

Early recognition and preoperative nutritional support in malnourished patients has been shown to reduce postoperative complications and improve outcomes in patients with gastrointestinal cancers [24] and in patients undergoing pancreaticoduodenectomy [25].

As this study is retrospective analysis, it forms a good basis for further investigation on the use of serum albumin as prognostic marker in prospective trials. There is also a need for prospective studies evaluating the effect of optimisation of serum albumin in the peri-operative period, by adequate nutritional supplementation on overall survival in ovarian cancer patients.

Conflict of interest None.

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