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ORIGINAL RESEARCH

Prognostic significance of preoperative serum albumin in epithelial ovarian cancer patients: a systematic review and dose–response meta-analysis of observational studies

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Purpose: To comprehensively assess the impact of preoperative serum albumin levels on survival of patients with epithelial ovarian cancer (EOC).

Materials and methods: Two independent researchers searched the PubMed, Embase, and Web of Science databases to identify relevant studies from inception to October 20, 2017. The studies were independently reviewed and those deemed eligible were selected based on predetermined selection criteria. Summarized HRs and 95% CIs were calculated for overall survival (OS) with a profile likelihood random-effects model.

Results: Twelve cohort studies comprising 3884 EOC patients were included for analysis. Comparison of the highest vs the lowest categories of preoperative serum albumin yielded a summarized HR of 0.63 (95% CI=0.45–0.88, I^2=88.8%). Although the results were robust in all subgroup analyses stratified by International Federation of Gynecology and Obstetrics (FIGO) stage, cutoff definition, geographical location, quality of study, number of EOC cases, follow-up time, and adjustments made for potential confounders, not all were statistically significant. Of note, dose–response analysis showed that for each 10 g/L increment in preoperative serum albumin level, the summary HR was 0.56 (95% CI=0.35–0.92, I^2=78.6%). No evidence of publication bias was detected by funnel plot analysis and formal statistical tests. Sensitivity analyses showed no important differences in the estimates of effects.

Conclusion: The present meta-analysis suggests that preoperative serum albumin can be used as an independent prognostic predictor of OS in EOC patients. Since the included studies had high heterogeneity and retrospective designs, these results require further validation with prospective cohort trials enrolling larger patient populations with longer follow-up examinations.

Keywords: albumin, meta-analysis, ovarian cancer, preoperative, prognosis

Introduction

Ovarian cancer accounted for an estimated 2,30,000 new diagnoses and 1,50,000 deaths worldwide in 2012.[1] Epithelial ovarian cancer (EOC) is the most common histological type of this disease. However, due to presentation at a late stage of disease and lack of specific symptoms, half of these patients experience recurrence within 16 months and the 5-year overall survival (OS) rate is <50%.[2–5] Advanced-stage disease is frequently related to ascites formation, nutritional deficits, weight loss, and poor patient performance. Various prognostic markers, including serum albumin, total protein, transferrin, and hemoglobin levels, are used to evaluate nutritional status in patients with gynecological cancers.[6]

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Albumin is the most abundant plasma protein in humans, accounting for 50%–65% of total serum protein[7] and is produced, but not stored, in the liver, with almost 60% present in the extravascular space.[8] Albumin plays a key role in maintaining colloid osmotic pressure and acts as a transport vehicle for intrinsic metabolites, drugs, and antioxidative agents.[9] Malignant disease has been shown to be associated with low albumin levels due to inhibitory effects on its synthesis by the liver[10] and sequestration in ascites or pleural effusion. The rate of albumin synthesis is associated with nutritional and disease states[11] and has been described as a crucial parameter of long-standing malnutrition.[12] These previous experimental studies raised concern as to whether preoperative serum albumin is associated with increased mortality in EOC patients. However, the evidence from previous observational studies is controversial,[8,12–22] as some studies have suggested that lower preoperative serum albumin was associated with decreased mortality of EOC,[8,12–16,19,21,22] while others failed to find any evidence of such an association.[17,18,20]

Therefore, to help reconcile these issues, the aim of this systematic review and meta-analysis of all relevant observational studies was to determine the effect of preoperative serum albumin level on survival of patients with EOC.

Patients and methods

Data sources and searches

The reporting standards of the Meta-Analysis of Observational Studies in Epidemiology group for systematic reviews and meta-analyses of nonrandomized controlled trials were followed.[23] Two independent researchers (L-NG and FW) searched the PubMed, Embase, and Web of Science databases to identify relevant studies from inception to October 20, 2017, without language restrictions. The following search keywords and terms were used: ("serum albumin" OR "nutrition" OR "serum proteins" OR "hypoalbuminemia" OR "hyperalbuminemia") AND ("ovary" OR "ovarian") AND ("cancer" OR "neoplasms" OR "carcinoma" OR "tumor") AND ("survival" OR "mortality" OR "prognosis").

Study selection

NoteExpress Research & Reference Manager software was used to identify and remove duplicate records. Subsequently, two researchers (L-NG and FW) independently checked the titles and abstracts of the retrieved articles for relevancy and then examined the full-text articles. Discrepancies were solved through discussion or, if necessary, arbitration by a third reviewer. The following inclusion criteria were used: 1) observational study design; 2) studies investigated the relationship of preoperative serum albumin with progression-free survival and OS of EOC patients; and 3) studies that included HRs or relative risk analyses with 95% CIs or provided data allowing the calculation of the risk estimates and 95% CIs. The following exclusion criteria were used: 1) randomized controlled trials, ecological studies, case–control studies, reviews without original data, editorials, commentaries, meeting abstracts, and case reports and 2) studies that reported risk estimates without 95% CI (eg, studies that could not be included in the statistical summary).

Data abstraction and risk of bias assessment

For each study selected for inclusion, two researchers (L-NG and FW) independently extracted data using a pilot-tested standardized form in Excel format (Microsoft Corporation, Redmond, WA, USA). The following data were collected: name of first author, year of study, country, number of cases and events, characteristics of patients, characteristics and unit of exposure, outcome, risk estimate, study-specific adjusted risk estimates with 95% CIs, and adjustment for potential confounder information, if applicable.

The Newcastle–Ottawa quality assessment scale for cohort studies was used to assess the risk of bias of the selected studies.[24–28] Subsequently, studies that achieved a full rating in at least two categories of selection, comparability, or outcome assessment were considered to have a low risk of bias.[29]

Statistical analyses

To unify the comparison, the effective-count method proposed by Hamling et al[30] was used to recalculate the HRs of studies that did not use the category with the lowest level of serum albumin as the reference[12,15–17] as well as those that only provided the results of dose–response analysis instead of the highest compared with the lowest category.[20,22] Overall, summary estimates were calculated using inverse variance-weighted random-effects meta-analysis. Individual HR estimates and summary estimates are displayed graphically as forest plots. Heterogeneity across the studies was quantified using the I^2 statistic, which indicates high heterogeneity when I^2>75%[31] and visually depicted using a Galbraith plot.[32] Furthermore, the sequential exclusion strategy propsed by Patsopoulos et al was used to examine

whether the overall estimates were influenced by the substantial heterogeneity observed.[33] Prespecified subgroup analyses were conducted according to the International Federation of Gynecology and Obstetrics (FIGO) stage (all vs III–IV), cutoff definition (hypoalbuminemia vs others), geographical location (Asia, Europe, and America), quality of study (low vs high risk), median number of EOC cases (≥250 vs <250), median follow-up time (≥2 vs <2 years), and adjustments made for potential confounders (including age at diagnosis, FIGO stage, grade, performance status, residual disease, and ascites). Heterogeneity between subgroups was evaluated by meta-regression analysis. A funnel plot was generated, and the Begg and Mazumdar[34] and Egger et al[35] methods were applied to examine small study biases (eg, publication bias). To assess the effect of individual studies on the estimated relative risk, sensitivity analysis was conducted in which the summarized risk estimates were recalculated by omitting one study at a time. All statistical analyses were performed using Stata 12.0 software (Stata LLC, College Station, TX, USA).

Results

Characteristics and quality assessment of the retrieved studies

The initial searches of the databases returned 9497 articles. After screening the titles and abstracts, 23 articles qualified for a full-text review (Figure 1). Finally, 12 cohort studies[8,12–21,36] were included in the present analysis.

Table 1 presents the key characteristics of the included studies. These studies were published from 1994 to 2017 and included a total of 3884 EOC patients with a range of 78–1189 cases in each study. Most (7/12, 58.3%) of the included studies were conducted in Europe,[8,15,16,18,20–22] while 4/12 (33.3%) were conducted in Asia,[12–14,17] and 1/12 (8.3%) was conducted in the USA.[19] Serum albumin was a categorical variable in 9/12 (75.0%) studies[8,12,14–19,21] and a continuous variable in 3/12 (25.0%) studies.[13,20,22]

According to the quality assessment criteria, 10 studies[8,12–17,19–21] were graded as low risk and two studies[18,22] as high risk (Table 2). Additionally, based on adjusted

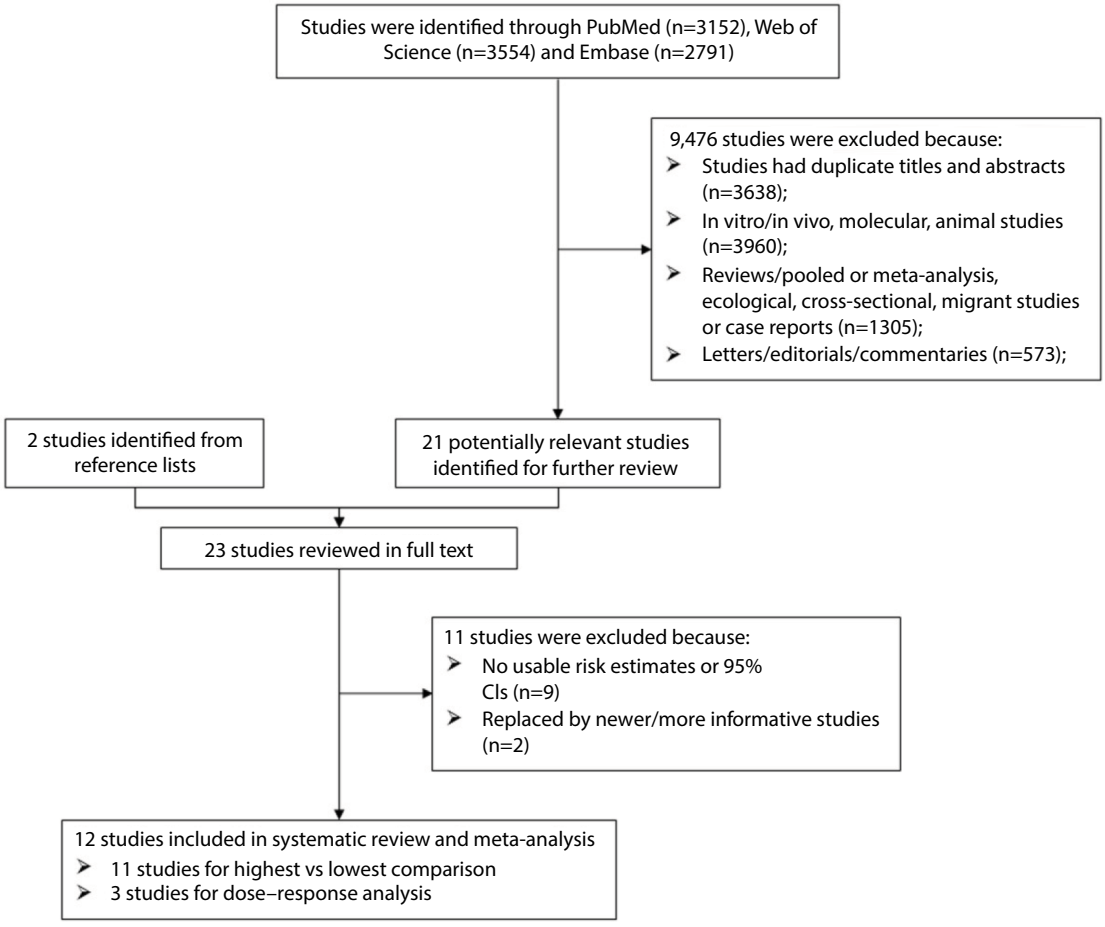

Figure 1 Selection of studies for inclusion in the present meta-analysis.

Table 1 Characteristics of studies included in the meta-analysis

Study, country	Study design	No. of case	Patient characteristics	Exposure characteristics (unit)	Outcome	Hazard ratio (95% CI)	Adjustment for potential confounders
Ayhan et al,[12] 2017, Turkey	Retrospective	337	All	Category (<32.5 vs ≥32.5) (g/L)	OS	2.6 (2.1–3.1)	Age, FIGO stage, histology, grade, LVI, para-aortic lymph node involvement, lymph node involvement, CA-125, and ascites
Liu et al,[13] 2017, China	Retrospective	200	All	Continuous (g/L)	OS	0.93 (0.89–0.97)	None
Zhang et al,[14] 2017, China	Retrospective	155	Clear cell	Category (>40 vs ≤40) (g/L)	PFS OS	0.49 (0.27–0.91) 0.41 (0.23–0.73)	FIGO stage, residual disease, preoperative ascites, neutrophil-to-lymphocyte ratio, endometriosis
Tinquaut et al,[15] 2016, France	Retrospective	266	Stage III–IV	Category (<35 vs ≥35) (g/L)	OS	2.00 (1.30–3.00)	Depressed, FIGO stage, BMI, and trial value
Ataseven et al,[16] 2015, Germany	Retrospective	604	All	Category (≤35 vs >35) (g/L)	OS	2.20 (1.60–3.00)	Age, PS, FIGO stage, residual disease, grade, and histology
Zhang et al,[17] 2015, China	Retrospective	190	All	Category (≤40 vs >40) (g/L)	PFS OS	0.54 (0.39–0.76) 0.43 (0.29–0.64)	None
Asher et al,[8] 2012, UK	Retrospective	235	All	Category (>35 vs <25) (g/L)	OS	0.27 (0.14–0.55)	Age, FIGO stage, residual disease, and grade
Sharma et al,[18] 2008, UK	Retrospective	154	Stage III–IV	Category (≥35 vs <35) (g/L)	OS	1.71 (0.92–3.18)	None
Alphs et al,[19] 2006, USA	Retrospective	78	All	Category (≥3.7 vs <3.7) (g/dL)	OS	0.58 (0.42–0.79)	Age, race, BMI, Charlson comorbidity index, performance status, surgeon, intraoperative blood transfusion, tumor size, intraoperative blood loss, and ascites removed
Clark et al,[20] 2001, UK	Retrospective	1189	All	Continuous (g/L)	OS	0.98 (0.96–1.00)	Age, FIGO stage, grade, histology, ascites, performance status, debulking, and log alkaline phosphatase
Warwick et al,[21] 1995, UK	Retrospective	362	All	Category (>35 vs ≤35) (g/L)	OS	0.73 (0.55–0.98)	PS and residual disease
Parker et al,[22] 1994, UK	Retrospective	114	All	Continuous (g/L)	OS	0.91 (0.86–0.96)	FIGO stage

Abbreviations: BMI, body mass index; CA-125, carbohydrate antigen-125; FIGO, International Federation of Gynecology and Obstetrics; PFS, progression-free survival; PS, performance status; OS, overall survival; LVI, lymphovascular invasion.

confounders, five studies[8,12,16,19,20] met our criteria for adequate adjustment, while the other seven[13–15,17,18,21,22] did not adequately adjust for potential confounders.

Preoperative serum albumin and OS of EOC patients (highest vs lowest category)

Eleven studies[8,12,14–22] reported data of the association between preoperative serum albumin and OS of EOC patients. Comparison of the highest vs the lowest categories of serum albumin yielded a summarized HR of 0.63 (95% CI=0.45–0.88; Figure 2), with significant heterogeneity (I^2=88.8%; Figure S1). There was no evidence of publication bias based on visual inspection of funnel plots (Figure S2) or according to the Begg's (p=0.88) or Egger's tests (p=0.33).

When studies[12,17,21] contributing the largest amount to heterogeneity until I^2 was <50% were sequentially excluded, the summarized HR for outcomes (HR=0.55, 95% CI=0.46–0.65, I^2=34.9%) were similar to the main results.

Table 2 Methodological quality of studies included in the meta-analysis

Study, year	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor[a]	Assessment of outcome	Follow-up long enough for outcomes to occur[b]	Adequacy of follow-up of cohorts[c]
Ayhan et al,[12] 2017	*	*	*	*	**	*	*	*
Liu et al,[13] 2017	*	*	*	*	–	*	*	*
Zhang et al,[14] 2017	–	*	*	*	–	*	*	*
Tinquaut et al,[15] 2016	*	*	*	*	*	*	*	*
Ataseven et al,[16] 2015	*	*	*	*	**	*	*	*
Zhang et al,[17] 2015	*	*	*	*	–	*	*	*
Asher et al,[8] 2012	*	*	*	*	**	*	*	*
Sharma et al,[18] 2008	*	*	*	*	–	*	–	*
Alphs et al,[19] 2006	*	*	*	*	**	*	–	*
Clark et al,[20] 2001	*	*	*	*	**	*	*	*
Warwick et al,[21] 1995	*	*	*	*	*	*	*	*
Parker et al,[22] 1994	*	*	*	*	*	*	–	*

Notes: A study could be awarded a maximum of one star for each item except for the item Control for an important factor or an additional factor. The definition/explanation of each column of the Newcastle–Ottawa Scale is available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.[46] [a]A maximum of two stars could be awarded for this item. Studies that controlled for age at diagnosis, International Federation of Gynecology and Obstetrics stage, received one star, whereas studies that controlled for other important confounders such as residual disease received an additional star. [b]A cohort study with a median follow-up time ≥24 months was assigned one star. [c]A cohort study with a follow-up rate >75% was assigned one star.

Additionally, the summarized HR ranged from 0.55 (95% CI=0.43–0.70, I^2=75.6%; exclusion of Zhang et al[17]) to 0.68 (95% CI=0.48–0.95, I^2=89.3%; exclusion of Asher et al;[8] Figure S3). After excluding studies that failed to adjust for any potential confounders, the result was robust (HR=0.51, 95% CI=0.42–0.62), but with moderate heterogeneity (I^2=63.8%).

Table 3 shows the results of subgroup analyses. Although the direction of all subgroup analyses was consistent with the main finding, not all were statistically significant. Importantly, significant results were observed in studies adjusted for these potential confounders. Except for FIGO stage (p=0.015), analysis of meta-regression showed no association between OS and any of the nine subgroup factors (Table 3).

Dose–response analysis of preoperative serum albumin and OS of EOC patients

Only three studies provided data of dose–response analysis. The results showed that for each 10 g/L increment in preoperative serum albumin concentration, the summary HR was 0.56 (95% CI=0.35–0.92), with high heterogeneity (I^2=78.6%; Figure 3).

Discussion

The present systematic review and meta-analysis shows that a higher preoperative serum albumin level was associated with better survival of EOC patients. Notably, for each 10 g/L increment in preoperative serum albumin concentration, the survival of EOC patients increased by 44%.

Serum albumin concentration is an important laboratory measurement to evaluate the nutritional status of patients.[37,38] Hypoalbuminemia in cancer patients may result from malnutrition, low appetite, weight loss, and cachexia due to the host responses to the tumor and antitumor therapies.[12,14] Low intake of amino acids and a negative nitrogen balance and degradation in albumin synthesis are determinants of serum albumin levels.[12] It was reported that 24% of patients with gynecological cancers are malnourished, and those with EOC have the highest rate of malnutrition (67%).[12,37] On the other hand, it is well recognized that serum albumin level is closely related to inflammation, which is involved in all stages of EOC formation, including initiation, promotion, development, and progression.[39,40] An increased inflammatory response with the production of cytokines, such as interleukin-6 and tumor necrosis factor, is detected in many cancers, including EOC.[12,41–43]

Although the majority (9/12, 75%) of the included studies treated preoperative serum albumin as a categorical variable,

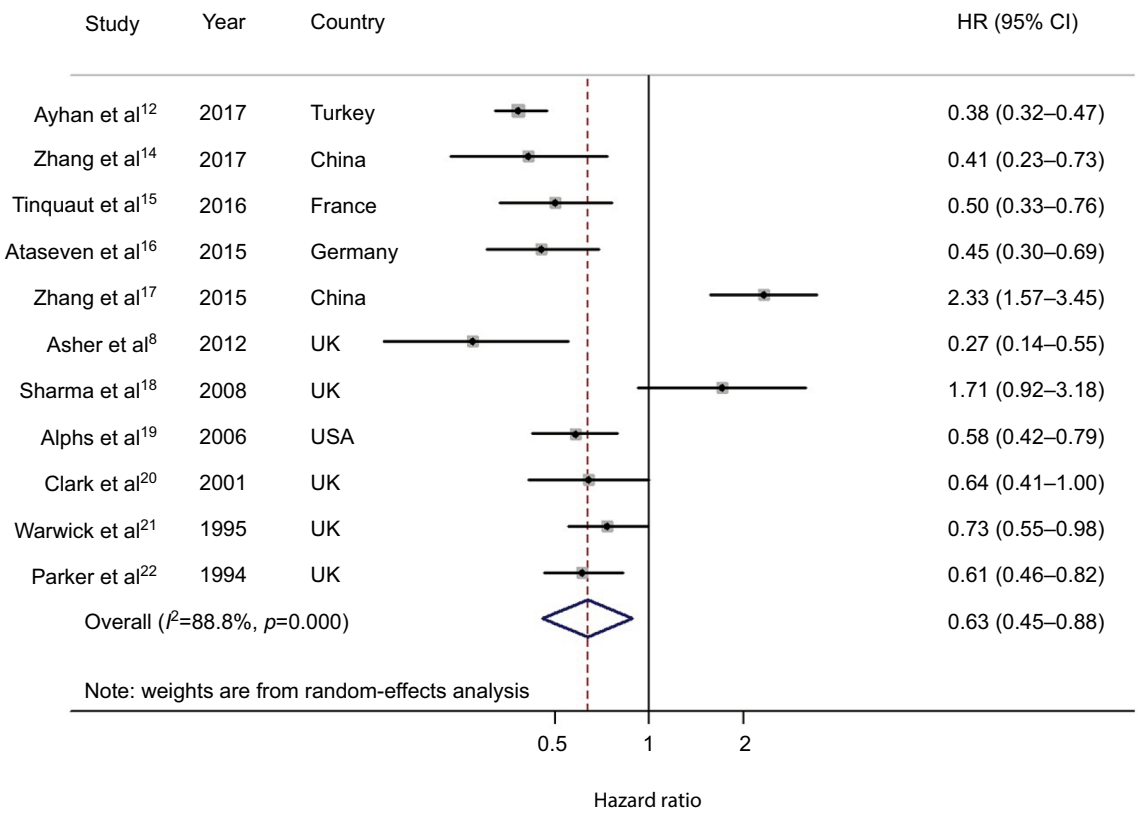

Figure 2 Forest plot (random-effects model) of preoperative serum albumin and overall survival of patients with epithelial ovarian cancer (highest vs lowest).
Notes: The squares indicate study-specific hazard ratio (size of the square reflects the study-specific statistical weight), the horizontal lines indicate 95% CIs, and the diamond indicates the summary hazard ratio estimate with its 95% CI.

the cutoff value for this biomarker varied among these studies due to methodological differences. Among these nine studies,[8,12,14–19,21] seven [8,14–18,21] defined a cutoff of preoperative serum albumin according to a state of hypoalbuminemia vs non-hypoalbuminemia. Additionally, other two studies[12,19] optimized preoperative serum albumin cutoff values using receiver operating characteristic curves or median values. Furthermore, the definition of hypoalbuminemia varied among these studies. For example, two studies conducted in China[14,17] set the cutoff value of hypoalbuminemia at 40 g/L, while studies conducted in France,[15] Germany,[16] and UK[21] set the value at 35 g/L. Interestingly, when summarizing these studies with a consistent definition of hypoalbuminemia, the summarized HR was 0.60 (95% CI=0.38–0.95, I^2=80.5%). However, it was unclear which method was most accurate, and none of the cutoff methods was a source of heterogeneity in the meta-regression analysis. Nevertheless, the heterogeneity between these two groups was slightly different (80.5% vs 92.6%, respectively). Future studies are needed to clarify which cutoff method provides the most accurate values to estimate the prognostic risk of EOC.

When interpreting these results, a good understanding of the strengths and limitations of this study is critical. The strengths of this systematic review include the systematic and rigorous approach used to identify observational studies investigating the impact of preoperative serum albumin on OS of EOC patients. Furthermore, the thoroughness of the study selection, data abstraction, and risk of bias assessment should also be mentioned. Of note, the present study provides the largest sample of women for the examination of the aforementioned associations reported to date and also provides the power to investigate whether these associations differed by important study characteristics as well as to conduct detailed sensitivity analyses. The results of these numerous preplanned subgroup and sensitivity analyses were consistent, which suggested that the results were robust. There were, however, some important limitations to consider. First, except for the study by Tinquaut et al[15] in a pooled analysis of three Phase II trials, the majority of the included studies were retrospective chart reviews, which may bear a potential risk of selection bias and information bias even though the data were obtained from hospital records. However, no other related prospective study

Table 3 Risk estimate summary of the association of serum albumin with overall survival of ovarian cancer patients (highest vs lowest)

Study characteristics	No. of studies	HR	95% CI	I^2 (%)	P_h [a]	P_h [b]
Overall	11	0.63	0.45–0.88	88.8	<0.001	
Subgroup analyses						
FIGO stage						
All	9	0.59	0.41–0.85	89.5	0.001	0.438
III–IV	2	0.90	0.27–3.02	90.4	<0.001	
Cutoff definition						
Hypoalbuminemia[c]	5	0.60	0.38–0.95	80.5	<0.001	0.815
Others	6	0.66	0.40–1.08	92.6	<0.001	
Geographical location						
Asia	3	0.71	0.21–2.42	97.0	<0.001	0.721
Europe	7	0.61	0.45–0.81	70.7	0.002	
America	1	0.58	0.42–0.79	N/A	N/A	
Quality						
Low risk	9	0.58	0.40–0.84	89.5	<0.001	0.313
High risk	2	0.98	0.36–2.69	88.5	0.003	
Number of cases						
<250	6	0.54	0.37–0.80	90.4	<0.001	0.398
≥250	5	0.76	0.43–1.32	82.7	<0.001	
Follow-up time (median)						
<2 years	3	0.78	0.48–1.27	90.8	<0.001	0.443
≥2 years	8	0.58	0.37–0.89	79.9	0.007	
Adjustment for confounders						
Age at diagnosis						
Yes	5	0.46	0.35–0.59	59.4	0.043	0.100
No	6	0.84	0.51–1.39	89.6	<0.001	
FIGO stage						
Yes	7	0.47	0.38–0.57	50.5	0.060	0.015
No	4	1.11	0.58–2.13	91.6	<0.001	
Grade						
Yes	4	0.43	0.32–0.56	50.5	0.109	0.107
No	7	0.79	0.52–1.21	88.2	<0.001	
Performance status						
Yes	4	0.61	0.50–0.74	18.4	0.299	0.807
No	7	0.66	0.38–1.13	92.9	<0.001	
Residual disease						
Yes	3	0.48	0.28–0.81	76.8	0.013	0.350
No	8	0.71	0.46–1.08	91.3	<0.001	
Ascites						
Yes	4	0.48	0.36–0.64	62.1		0.323
No	7	0.73	0.46–1.18	89.8	<0.001	

Notes: [a]*p*-value for heterogeneity within each subgroup. [b]*p*-value for heterogeneity between subgroups in a meta-regression analysis. [c]Studies with a consistent definition of hypoalbuminemia (<35 g/L).

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; N/A, not available.

was found through our search strategy. Second, the majority of results had high levels of heterogeneity, which was not unexpected, and might have been caused by differences in FIGO stage, cutoff definition, geographical location, study quality, number of cases, follow-up time, and adjustment for potential confounders. Specifically, the results of the meta-regression analysis showed statistical significance after adjustment for FIGO stage, which suggested that this factor might be a source of heterogeneity. Of note, moderate or low heterogeneity was observed after summarizing the studies adjusted for these potential confounders as well as excluding those that failed to adjust for potential confounders. Third, although preoperative serum albumin had a strong impact on the OS of EOC patients, residual confounding from unmeasured or incomplete variables could not be ruled out due to the inherit characteristics of meta-analysis of observational studies. Preoperative serum albumin concentrations are typically associated with other clinical and nonclinical characteristics, such as histology, FIGO stage, ascites, comorbidity, performance status, and weight loss.[12,36] Many, but not all, of the studies adjusted for

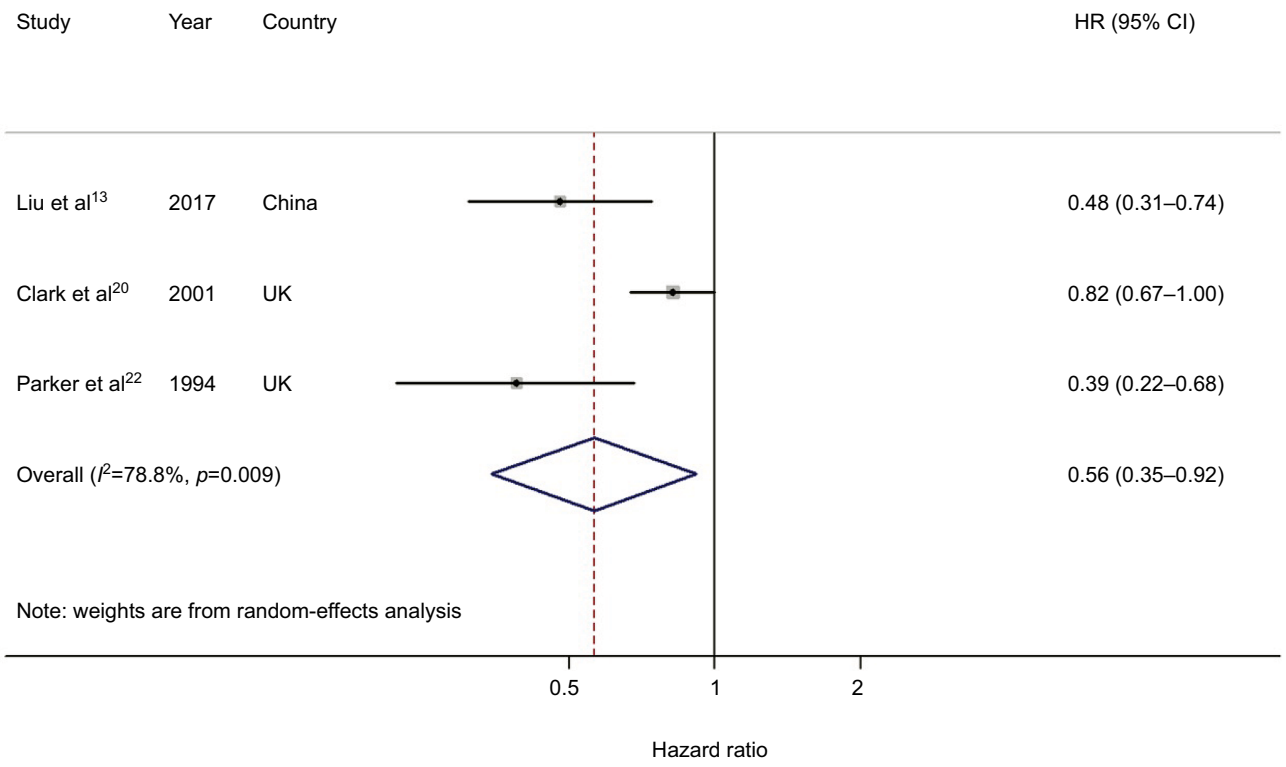

Figure 3 Forest plot (random-effects model) of dose–response analysis of the preoperative serum albumin (per 10 g/L increment) and overall survival of patients with epithelial ovarian cancer.
Notes: The squares indicate study-specific hazard ratio (size of the square reflects the study-specific statistical weight), the horizontal lines indicate 95% CIs, and the diamond indicates the summary hazard ratio estimate with its 95% CI.

potential confounding factors, although not all potential confounders were adjusted for in every study. Importantly, only one of the included studies[14] adjusted the primary analysis for systemic inflammatory response markers (eg, neutrophil to lymphocyte ratio, C-reactive protein, and absolute white blood cell count), which have been suggested as independent prognostic factors. Hence, further studies fully adjusted for these confounders are warranted. Fourth, few of the included studies treated preoperative serum albumin as a continuous variable in the primary multivariate analyses; therefore, it was not possible to evaluate dose–response associations between preoperative serum albumin and OS of EOC patients or to test whether a nonlinear association existed. Further studies with sufficient data to conduct dose–response analyses are warranted in the future.

Conclusion

The results of this dose–response meta-analysis suggest that higher preoperative serum albumin levels are associated with better prognosis of EOC patients. Preoperative serum albumin might be used for preoperative evaluation of EOC patients and for risk prediction in clinical practice. These findings were consistent with the 2002 American Society for Parenteral and Enteral Nutrition guidelines and the European guidelines, which recommend that cancer patients with severe nutritional risk should receive nutritional support for 1–2 weeks prior to a major surgery.[44,45]

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

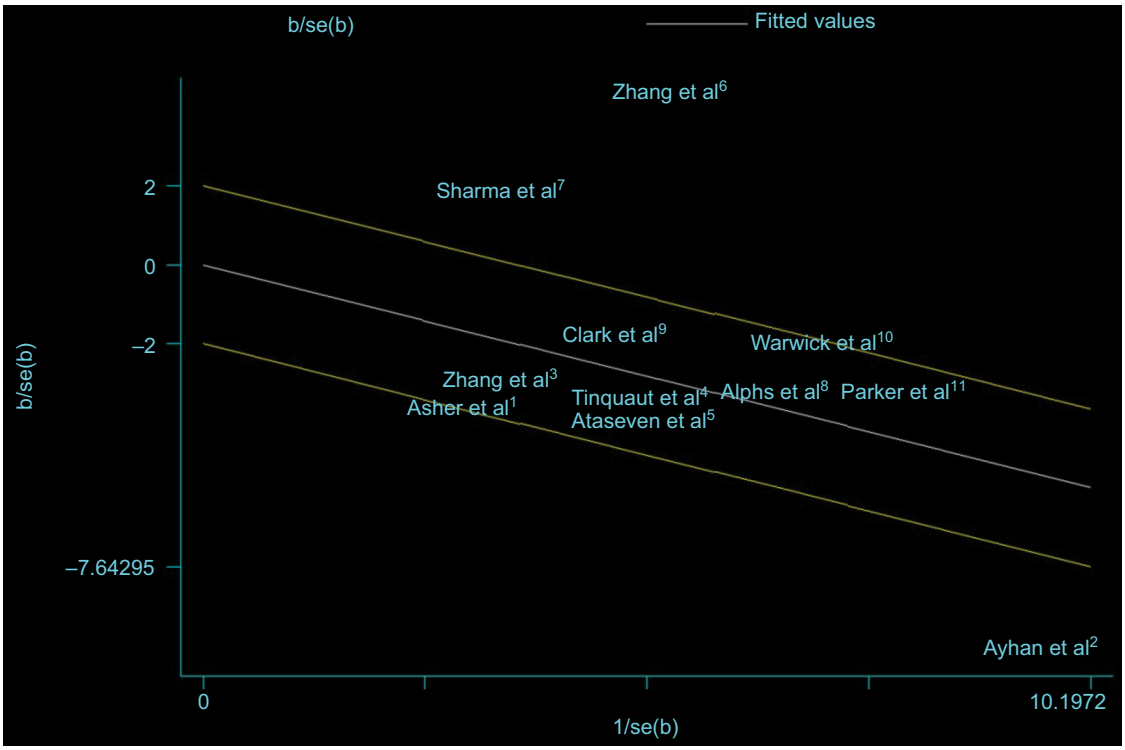

Figure S1 Galbraith plot corresponding to the relationship between pre-operative serum albumin and overall survival of patients with epithelial ovarian cancer.
Abbreviation: SE, standard error.

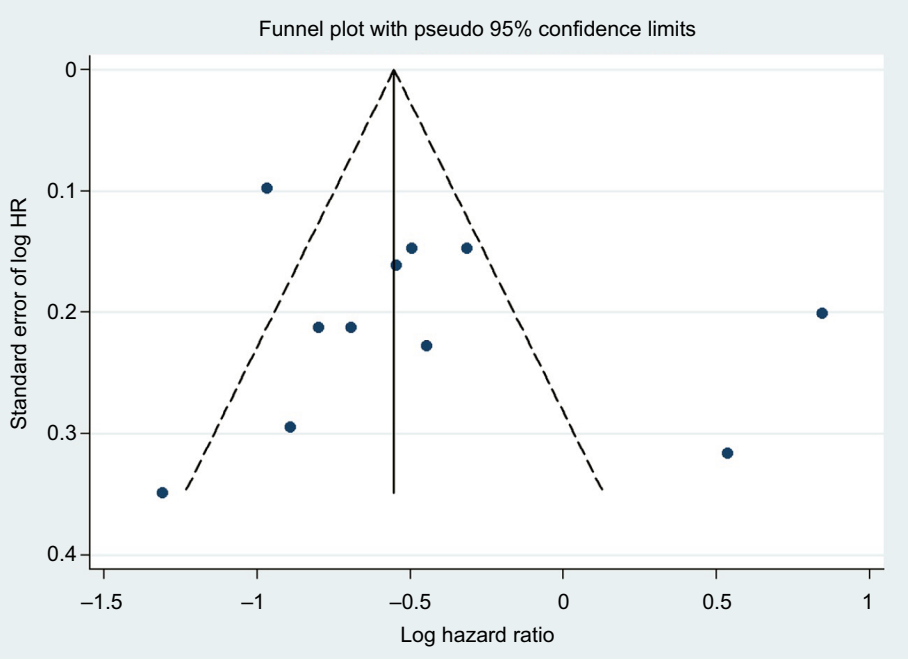

Figure S2 Funnel plots for detection for publication bias.
Abbreviations: HR, hazard ratio; SE, standard error.

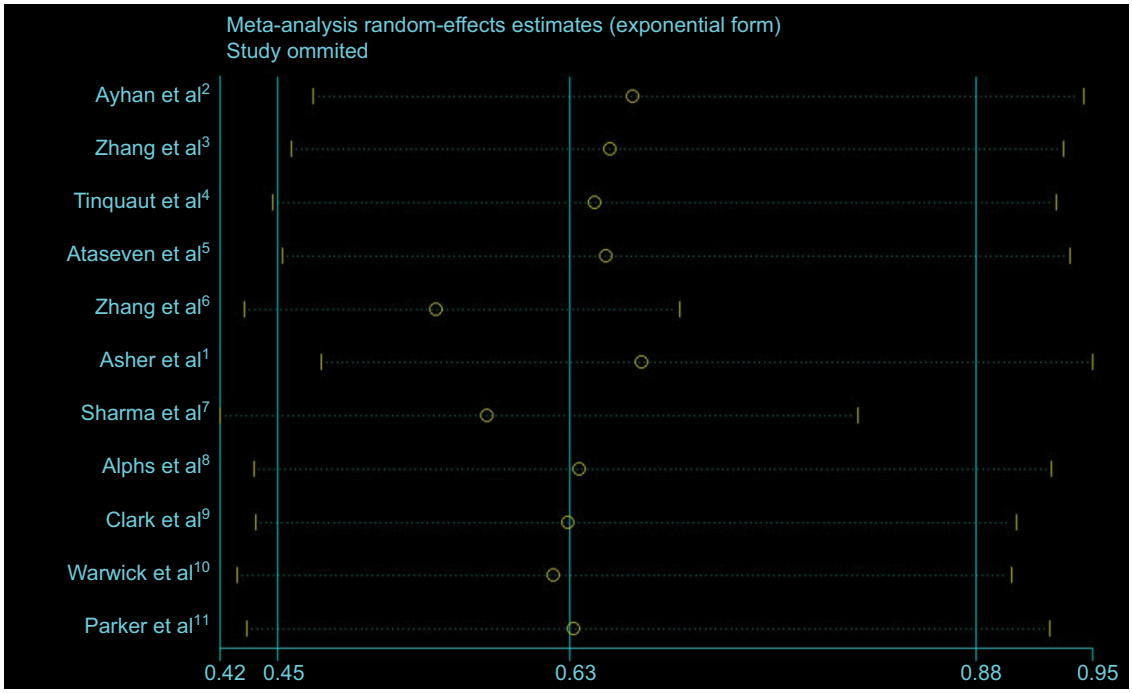

Figure S3 Sensitivity analysis of the association between pre-operative serum albumin and overall survival of patients with epithelial ovarian cancer.

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