ORIGINAL RESEARCH

The association of pretreatment serum albumin with outcomes in bladder cancer: a meta-analysis

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Background: Recently, numerous studies have shown that pretreatment serum albumin can be closely associated with the prognosis of patients with bladder cancer (BC). However, the conclusions regarding this issue are still conflicting. Hence, in this study, we performed a systematic review and meta-analysis to determine the prognostic significance of pretreatment serum albumin in BC patients.

Materials and methods: A systematic search was carried out in PubMed, Embase, and Web of Science. A total of 16 studies involving 13,917 patients were included in the current meta-analysis. hazard ratios (HRs) and 95% CIs were pooled to assess the intensity of association. Moreover, heterogeneity, sensitivity analysis and publication bias were explored. All statistical analyses were conducted by STATA 12.0.

Results: Our results suggested that a decreased pretreatment serum albumin level was closely related to a worse overall survival (HR 1.88, 95% CI 1.43, 2.48; $P<0.01$) and cancer-specific survival (HR 1.65, 95% CI 1.08, 2.52; $P=0.02$). In addition, from the results of this meta-analysis, it was also observed that a lower pretreatment serum albumin level was linked to higher incidence of postoperative 30-day complication (odds ratio [OR] 1.41, 95% CI 1.03, 1.91; $P=0.03$) and 90-day mortality (OR 2.51, 95% CI 1.82, 3.48; $P<0.01$). Furthermore, these findings were demonstrated to be reliable by our sensitivity and subgroup analysis stratified by ethnicity, analysis type, and cutoff value.

Conclusion: Our results revealed that a lower pretreatment serum albumin level yields a poor long-term prognosis and increases the risks of postoperative complication and mortality in BC patients and can be applied to risk stratification and individualized therapy in BC patients.

Keywords: albumin, prognosis, mortality, bladder cancer, meta-analysis

Introduction

Bladder cancer (BC), the most common urinary tract carcinoma, was reported to have an estimated 76,960 new cases and result in 16,390 deaths in the USA in 2016 alone.[1] BC is characterized with great heterogeneity, but it is still divided into two main subsets in clinical practice: non-muscle-invasive BC (NMIBC) and muscle-invasive BC (MIBC).[2] Although nearly 75% of BC patients are diagnosed as having NMIBC that only invades the mucosa or submucosa of bladder, approximately 50%–70% of NMIBC patients experience disease recurrence and about 10%–30% of NMIBC patients advance into MIBC that is rather aggressive and tends to metastasize.[3] Worse still, the majority of MIBC is related to high mortality, in spite of the improved therapeutic modalities available currently.[4] Thus, it is very urgent to develop prediction models to differentiating patients from diverse prognosis, and those with an adverse prognosis may benefit from early comprehensive therapy. Up to now, tumor stage, grade, and metastasis are considered as the main prognostic factors for BC. Nevertheless, the currently used

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system usually fails to precisely predict the prognosis of BC patients with disparate tumor backgrounds.[5] In this regard, novel biomarkers that can identify patients with unfavorable outcomes when applied alone, or combined with other clinicopathological characteristics, are needed to accurately guide clinical decisions.

Serum albumin is produced in the liver and occupies a large proportion of serum protein. The physiological serum level of albumin fluctuates from 3.5 to 5.0 g/dL in adults. Admittedly, the concentration of serum albumin inferior to 3.5 g/dL is defined as hypoalbuminemia.[6] Serum albumin is tightly correlated with the severity of malnutrition and is often applied to assessing nutritional status.[7] In addition, numerous studies have suggested that the level of serum albumin is also influenced by inflammatory response. Thus, serum albumin has the potential to be applied as a reliable biomarker of inflammation.[8,9] Particularly, malnutrition and chronic inflammation response often accelerate the progression of the disease by promoting the development of tumor cachexia,[10] which hints that serum albumin, as an indicator for the status of malnutrition and chronic inflammation, might be related to the prognosis in patients with cancer. Thus, in recent years, many studies were conducted to investigate the association between serum albumin and prognosis in various cancers, and the majority of studies indicated that the decreased pretreatment serum albumin is closely related to worse prognosis of tumor patients.[9,11–14] Specifically, some of these studies have focused on exploring the association of pretreatment serum albumin with the prognosis of BC patients.[15–31] Nevertheless, the prognostic value of pretreatment serum albumin in BC patients is inconsistent. Some studies showed that decreased pretreatment serum albumin was associated with worse prognosis of BC patients, but others indicated that there was no relationship between pretreatment serum albumin and prognosis of BC patients. Therefore, it is imperative to perform a meta-analysis to assess the prognostic significance of pretreatment serum albumin in BC patients.

Materials and methods
Data sources and search
A systematic search was carried out in PubMed, Embase, and Web of Science (up to November 12, 2017). The search strategy was generated by combining the following terms: "bladder cancer or bladder carcinoma or bladder tumor or cystectomy" and "albumin or hypoalbuminemia" and "prognos* or survival or outcome."

Study selection
The studies that met the following criteria were included: 1) the diagnosis of BC patients was histopathologically confirmed; 2) retrospective study or perspective study design; and 3) the relationship between preoperative serum albumin and long-term survival, short-term postoperative outcomes, or postoperative mortality should be analyzed, and full text of studies should be accessible to extract these data. In contrast, studies meeting the following criteria were excluded: 1) abstracts, case reports, reviews, editorials, or letters; 2) overlapping or duplicate data among studies; 3) studies about the BC patients who did not undergo radical surgical treatment; 4) studies focusing on the correlation between preoperative serum albumin and non-BCs. The language and region of publications were not restricted in this meta-analysis.

Data collection and quality evaluation
Data from eligible studies were extracted by two authors (Jialin Li and Yusheng Cheng) independently, and any divergence was addressed by the second coauthor (Guanghua Liu). Data extracted from eligible publications included the following: first author, publication year, country, case number, age, sex, treatment methods, median follow-up months, the cutoff value for pretreatment serum albumin, and the outcomes of our interest that included overall survival (OS), cancer-specific survival (CSS), postoperative 30-day complication (30dC), and 90-day mortality (90dM). Multivariate end points were preferred than univariate end points if both were reported in studies. If survival data were not provided directly in the eligible studies, described by a Kaplan–Meier curve, the Engauge Digitizer version 4.1 was applied to calculate and extract the hazard ratio (HR) and its 95% CI.[32] The Newcastle–Ottawa Scale (NOS)[33] was used to assess the quality of eligible publications. The scores of NOS ranged from 0 to 9, and in this meta-analysis, studies with scores of 6 or more were considered as high-quality publications.

Statistical analyses
The statistical processes of this meta-analysis were fulfilled using Stata version 12.0 (StataCorp LP, College Station, TX, USA). Synthesized HRs and their 95% CIs were used to assess the association of pretreatment serum albumin with OS and CSS. In addition, pooled odds ratios (ORs) and their 95% CIs were used to assess the relationship of pretreatment serum albumin with postoperative 30dC and 90dM. Heterogeneity among studies was assessed by Chi-square-based Q and I^2 tests.[34] If $I^2 > 50\%$ or $P < 0.01$, the heterogeneity of the synthesized data was considered statistically significant, and then a random-effects model was used; otherwise, fixed-effects model was conducted. Sensitivity analyses were carried out

to investigate the factors contributing to the heterogeneity and test the stability of the pooled results in this meta-analysis. Sensitive analysis was conducted by omitting each study.

Results
Study selection
The strategy of search and selection is shown in Figure 1. The initial literature search yielded 185 potentially relevant studies with 41 from PubMed, 81 from Embase, and 63 from Web of Science. Of all identified records, 27 duplicated articles were removed. In the full-text screening for remaining 158 publications, 126 articles were excluded, including reviews (n = 9), meeting abstracts (n = 26), irrelevant studies (n = 74), and no extracted data (n = 33). Finally, a total of 16 studies with 13,917 cases were included in this meta-analysis.[15–30]

Characteristics of eligible studies and quality assessment
Summary characteristics of eligible studies are presented in Table 1. The 16 included articles were published between 2011 and 2017. The region of studies included China (n = 2), Japan (n = 2), USA (n = 7), Canada (n = 1), UK (n = 1), France (n = 1), Egypt (n = 1), and Korea (n = 1). The cutoff value for pretreatment serum albumin varied from 3.5 to 4. The sample size of the included studies ranged from 31 to 5,568. The OS was analyzed in seven articles with 3,374 patients.[17,19,21–24,29] The CSS was investigated in five publications involving 1,086 patients,[16,21–23,26] 30dC was inquired into in seven articles with 11,589 patients,[15,17,18,20,23,25,30] and 90dM was explored in six studies with 8,523 patients.[15,17,18,23,27,28] The cutoff value of pretreatment serum albumin applied in most

publications was 3.5 g/dL (the lower limit of normal). Based on the NOS, most of the included studies scored ranging from 6 to 7 (Table 2), indicating that the quality of eligible studies was high.

Impact of pretreatment serum albumin on OS and CSS
A total of seven articles were included in the meta-analysis of OS in BC patients.[17,19,21–24,29] Because of the significant heterogeneity ($I^2 = 60.2\%$; $P < 0.01$), random-effects model was used to synthesize the HR for the impact of pretreatment serum albumin on OS. The result showed that patients with decreased pretreatment serum albumin had a significant shorter OS (HR 1.88, 95% CI 1.43, 2.48; $P < 0.01$; Figure 2). Regarding the CSS, five publications provided the available data for pooling analysis,[16,21–23,26] which indicated that low level of pretreatment serum albumin was also significantly correlated with worse CSS (random-effects model: HR 1.65, 95% CI 1.08, 2.52; $P = 0.02$; heterogeneity: $I^2 = 86.7\%$; $P < 0.01$; Figure 3).

Impact of pretreatment serum albumin on postoperative 30dC and 90dM
In the eligible studies, seven inquired into the relationship between preoperative serum albumin and 30dC in BC patients.[15,17,18,20,23,25,30] Since the significant heterogeneity exists among the included articles ($P < 0.01$; $I^2 = 80.9\%$), random effects were carried out to pool the data. After synthesizing the data, we found that a low pretreatment serum albumin was closely related to worse 30dC (OR 1.41, 95% CI 1.03, 1.91; $P = 0.03$; Figure 4). In addition,
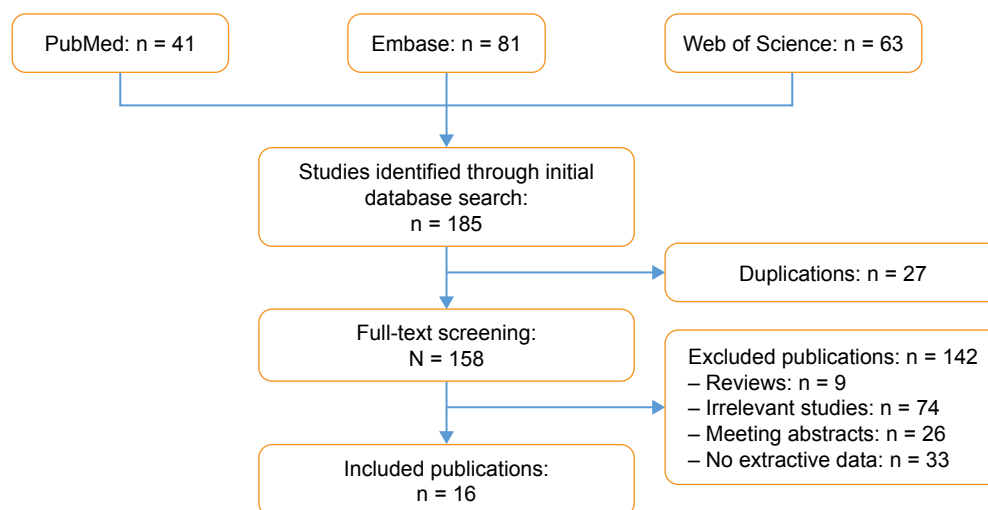

Figure 1 Flow diagram of study selection.

Table 1 The main characteristics of the included studies

Study	Country	Tumor type	Case number (LSA/HSA)	Age (years)	Sex (male/ female)	Surgical treatment	Follow-up (months)	Survival analysis	Cutoff value of serum albumin (g/dL)
Caras et al[15]	USA	BC	1,292/4,282	65	4,228/1,340	RC	1	NR	3.5
Chan et al[16]	China	BC	62/55	68 ± 10	99/18	RC	31	CSS, OCS, OS	3.9
Djaladat et al[17]	USA	BC	197/1,274	67	1,154/317	RC	12.4	OS	3.5
Garg et al[18]	USA	BC	150/947	68	831/266	RC	25.2	NR	4
Hinata et al[19]	Japan	BC	NR	68.6	575/155	RC	52	OS	3.5
Johnson et al[20]	USA	BC	102/587	73	530/159	RC	1	NR	3.5
Krane et al[21]	USA	BC	NR	67.4	55/13	RC	25	OS, CSS	3.5
Ku et al[22]	Korea	BC	NR	65.1	362/57	RC	37.7	OS, CSS	3.5
Lambert et al[23]	UK	BC	31/156	67.4	153/34	RC	26.2	OS, CSS	3.5
Laurent et al[24]	France	BC	95/98	75.2	164/29	RC	9.1	OS	3.5
Lavallee et al[25]	Canada	BC	341/1,090	70	1,819/484	RC	NR	NR	NR
Liu et al[26]	China	BC	129/167	61.71	250/45	RC	72	CSS	4.0
Morgan et al[27]	USA	BC	30/139	78.8	122/47	RC	3	NR	3.7
Mursi et al[28]	Egypt	BC	24/7	58.4	22/9	RC	3	NR	3.5
Nakagawa et al[29]	Japan	BC	NR	69	248/58	RC	6.8	OS	3.5
Sharma et al[30]	USA	BC	NR	70.1	209/65	RC	NR	NR	4.0

Abbreviations: LSA, low serum albumin; HSA, high serum albumin; BC, bladder cancer; CSS, cancer-specific survival; OS, overall survival; RC, radical cystectomy; NR, not reported.

six publications involved 90dM.[15,17,18,23,27,28] The results from meta-analysis of six publications suggested that a decreased preoperative serum albumin was significantly related to worse 90dM (OR 2.51, 95% CI 1.82, 3.48; $P < 0.01$; heterogeneity: $P = 0.295$, $I^2 = 18.2\%$; Figure 5).

Subgroup analysis and sensitivity analysis

Taking into account that significant heterogeneity existing among the included studies might challenge the reliability and robustness of the results from this meta-analysis, subgroup analysis and sensitivity analysis were performed to explore the potential source of heterogeneity and meanwhile determine whether the results of this meta-analysis were reliable. Sensitivity analysis was conducted by omitting each study. The results showed that the pooled HRs for OS (Figure 6) and CSS (Figure 7) as well as ORs for 30dC (Figure 8) and 90dM (Figure 9) did not alter significantly, which demonstrated the strength of our findings. In addition, the significance of pretreatment serum albumin was further evaluated via subgroup analysis according to ethnicity, analysis type, and cutoff value, and its results indicated that our findings were reliable (Table 3).

Discussion

To the best of our knowledge, our meta-analysis is the first comprehensive study to systematically assess the prognostic significance of pretreatment serum albumin in BC patients. From the final results of this meta-analysis, there was a substantial association between decreased pretreatment serum albumin level and unfavorable long-term survival of BC patients with a pooled HR of 1.78 (95% CI 1.39–2.28) for OS and 1.65 (95% CI 1.08–2.52) for CSS. In addition, our meta-analysis also demonstrated that decreased pretreatment serum albumin level was closely correlated with higher incidence of postoperative 30dC and 90dM. Furthermore, in general, our subgroup analysis and sensitivity analysis also validated the robust of the combined HR.

Pretreatment serum albumin is closely correlated with the outcomes of BC and other malignancies, but the underlying mechanisms for this have not been fully elucidated. However, the association of nutrition and inflammation with serum albumin has been considered as one of the explanations for this. The malnutrition and chronic inflammation often occur in the initiation and progression of malignant tumors, and they can contribute to the worsening of cancer patients and finally lead to cachexia, which will increase the risk of posttreatment complications and mortality and shorten the long-term survival. The loss of appetite and the consumption of body component usually result in malnutrition in cancer patients, and this is mirrored by hypoalbuminemia and pitting edema. The systematically chronic inflammation in malignant tumor patients also affects the serum albumin level. Due to the inflammatory response to cancer, many pro-tumor cytokines, including tumor necrosis factor, interleukin-1, interleukin-6, and interleukin-8, are released, which can directly suppress the function of hepatic cells to generate

Table 2 The NOS quality assessment of the enrolled studies

Study	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of cohorts based on the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	
Caras et al[15]	★	★	★	★	★☆	☆	★	★	7
Chan et al[16]	☆	★	★	★	★☆	★	★	☆	6
Djaladat et al[17]	★	★	☆	★	★☆	★	★	★	7
Garg et al[18]	★	★	☆	★	★☆	★	★	★	7
Hinata et al[19]	★	☆	★	★	★☆	★	★	★	7
Johnson et al[20]	★	☆	★	★	★☆	★	★	★	7
Krane et al[21]	★	☆	★	★	★☆	★	★	☆	6
Ku et al[22]	★	☆	★	★	★☆	★	★	★	7
Lambert et al[23]	☆	★	★	★	★☆	★	★	★	7
Laurent et al[24]	★	★	★	★	★☆	★	☆	★	7
Lavallee et al[25]	★	★	☆	★	★☆	★	★	★	7
Liu et al[26]	☆	★	★	★	★☆	★	☆	★	6
Morgan et al[27]	☆	★	★	★	★☆	★	★	★	7
Mursi et al[28]	☆	★	☆	★	★☆	★	☆	★	5
Nakagawa et al[29]	★	★	★	★	★☆	★	★	☆	7
Sharma et al[30]	☆	★	☆	★	★☆	★	★	★	6
Taguchi et al[31]	★	★	☆	★	★☆	★	★	★	7

Notes: ★ Represents one score and ☆ represents no score in corresponding items.
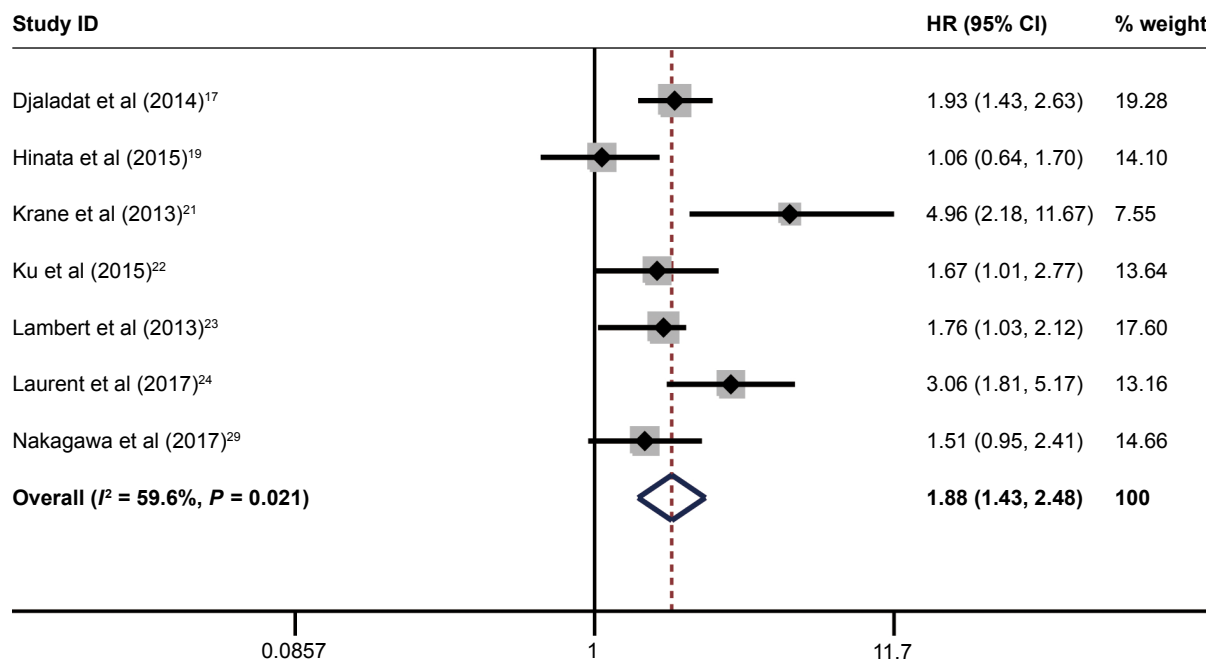**Abbreviation:** NOS, Newcastle–Ottawa Scale.

Study ID		HR (95% CI)	% weight
Djaladat et al (2014)[17]		1.93 (1.43, 2.63)	19.28
Hinata et al (2015)[19]		1.06 (0.64, 1.70)	14.10
Krane et al (2013)[21]		4.96 (2.18, 11.67)	7.55
Ku et al (2015)[22]		1.67 (1.01, 2.77)	13.64
Lambert et al (2013)[23]		1.76 (1.03, 2.12)	17.60
Laurent et al (2017)[24]		3.06 (1.81, 5.17)	13.16
Nakagawa et al (2017)[29]		1.51 (0.95, 2.41)	14.66
Overall (I^2 = 59.6%, *P* = 0.021)		1.88 (1.43, 2.48)	100

0.0857   1   11.7

Figure 2 The prognostic significance of low pretreatment serum albumin level on OS in BC.
Note: Weights are from random-effects analysis.
Abbreviations: BC, bladder cancer; HR, hazard ratio; OS, overall survival.

albumin.[35,36] In addition, the tumor necrosis factor produced by tumor cells augments the permeability of capillaries, leading to the direct loss of albumin from the circulatory system.[37] Furthermore, micro-metastases located in liver during the late stage of cancers are capable of impairing the liver function, which also inhibits the synthesis of albumin.[35] Hence, the decreased pretreatment serum albumin level is related to the worse prognosis of cancer patients, and consequently it might be an effective and inexpensive prognostic biomarker for cancer patients.
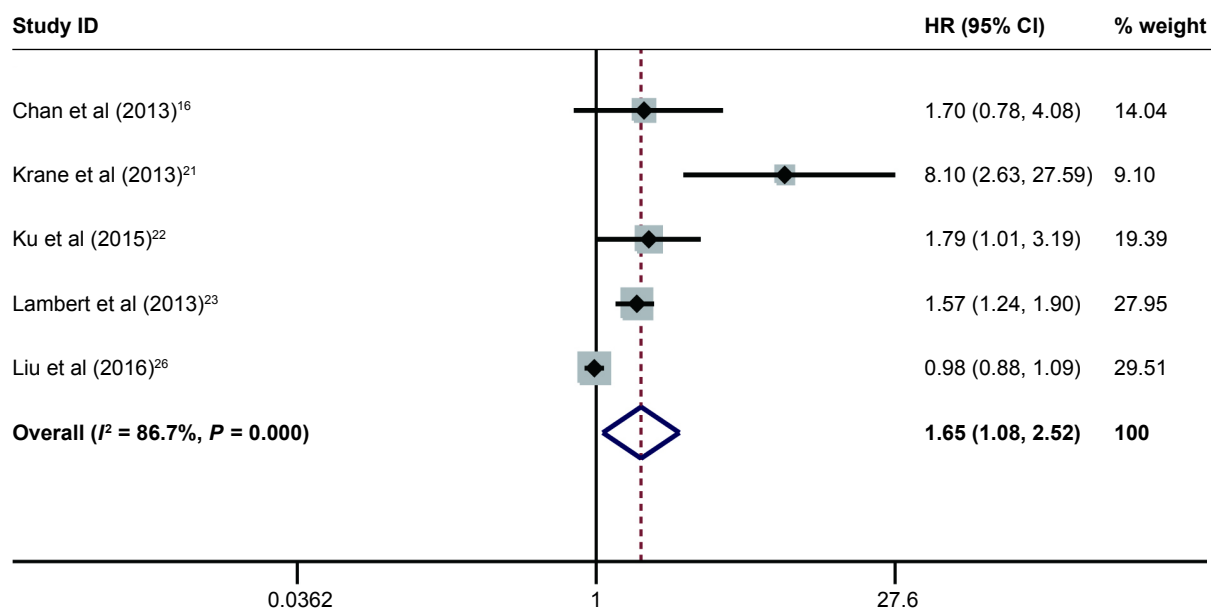
Study ID		HR (95% CI)	% weight
Chan et al (2013)[16]		1.70 (0.78, 4.08)	14.04
Krane et al (2013)[21]		8.10 (2.63, 27.59)	9.10
Ku et al (2015)[22]		1.79 (1.01, 3.19)	19.39
Lambert et al (2013)[23]		1.57 (1.24, 1.90)	27.95
Liu et al (2016)[26]		0.98 (0.88, 1.09)	29.51
Overall (I^2 = 86.7%, *P* = 0.000)		1.65 (1.08, 2.52)	100

0.0362   1   27.6

Figure 3 The prognostic significance of low pretreatment serum albumin level on CSS in BC.
Note: Weights are from random-effects analysis.
Abbreviations: BC, bladder cancer; CSS, cancer-specific survival; HR, hazard ratio.
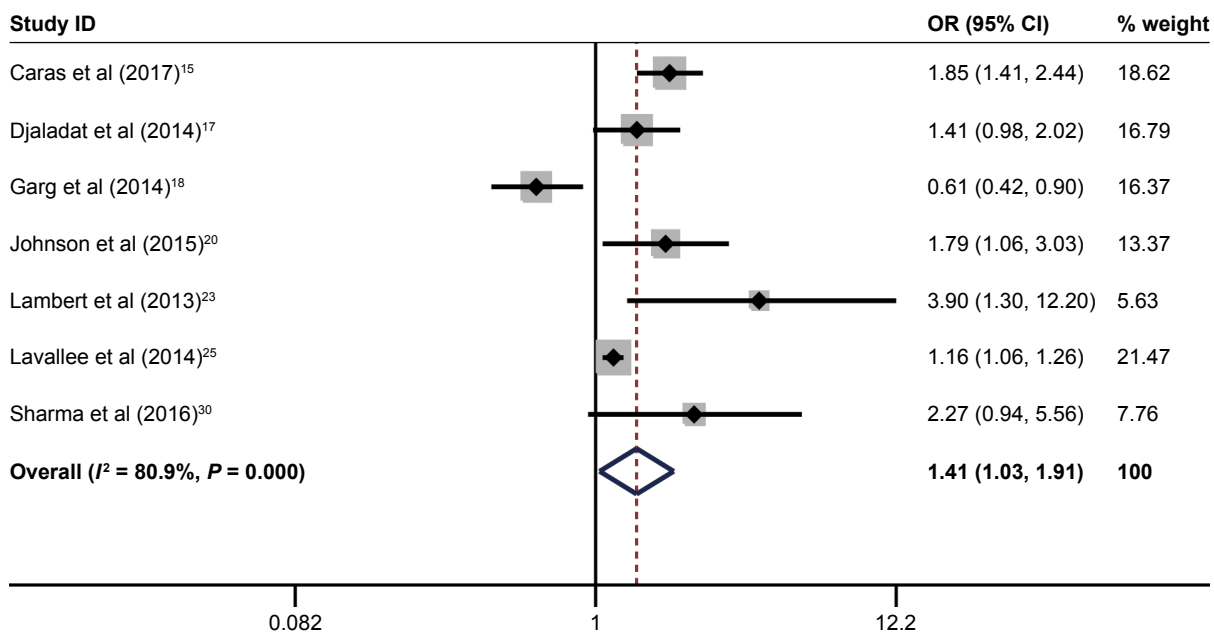
Figure 4 The impact of pretreatment serum albumin on postoperative 30dC.
Note: Weights are from random-effects analysis.
Abbreviations: 30dC, 30-day complication; OR, odds ratio.

Although serum albumin is an inexpensive and easily obtainable index for the prognosis in BC patients, some issues should be noticed when it is applied to clinical practice. Under some conditions, malnutrition might not be reflected by the concentration of serum albumin. For instance, when cancer patients suffered from dehydrated conditions, the serum albumin level will be normal and even increased, even if they have cancer-related malnutrition.[38,39] Besides, dietary changes and other factors that are not specifically associated with cancers can also influence the concentration of serum albumin. Therefore, if the interference of these factors is excluded, pretreatment serum albumin would be a reliable
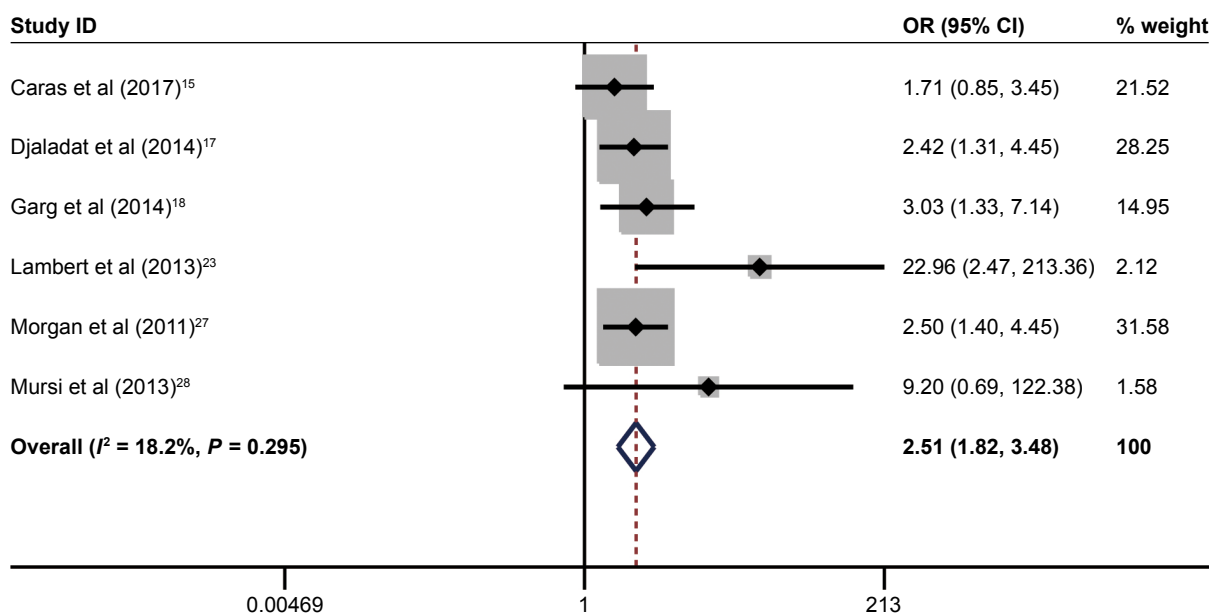
Figure 5 The impact of pretreatment serum albumin on postoperative 90dM.
Abbreviations: 90dM, 90-day mortality; OR, odds ratio.

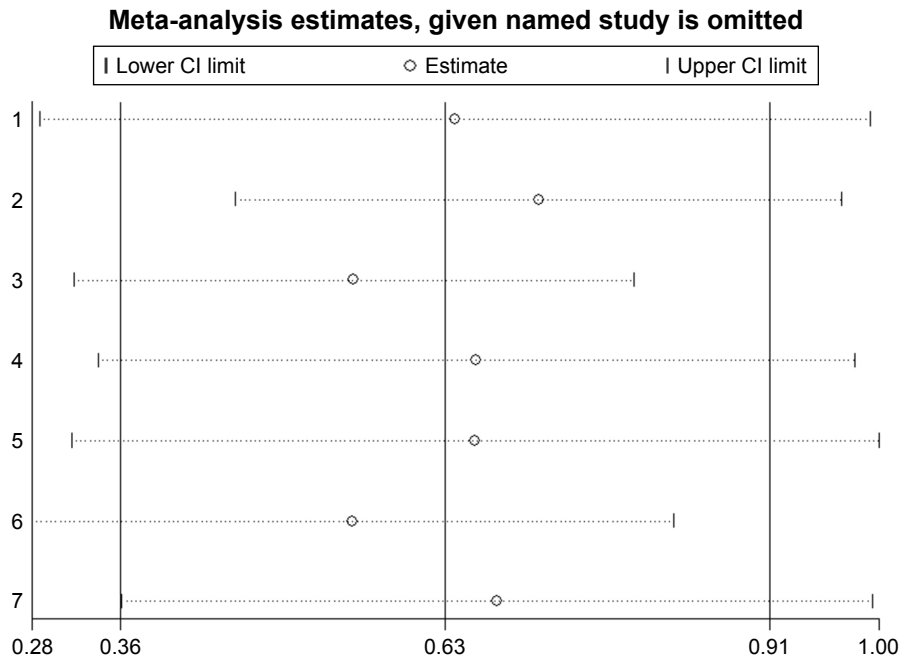## Meta-analysis estimates, given named study is omitted

Figure 6 The results of sensitivity analysis of the pooled HR for OS.
Abbreviations: HR, hazard ratio; OS, overall survival.

prognostic predictor in BC patients. For instance, considering those limitations in the clinical practice, recently, to improve the accuracy of risk stratification for cancer patients, many studies have investigated the prognostic values of the combination of serum albumin and other serum markers in cancer patients. For instance, one study suggested that the albumin/globulin ratio combining the preoperative serum albumin and globulin levels can effectively stratify BC patients by the prognostic risks.[26]

The results from our meta-analysis might be challenged by several limitations. First, the majority of the included studies were retrospective, which might cause bias in patient
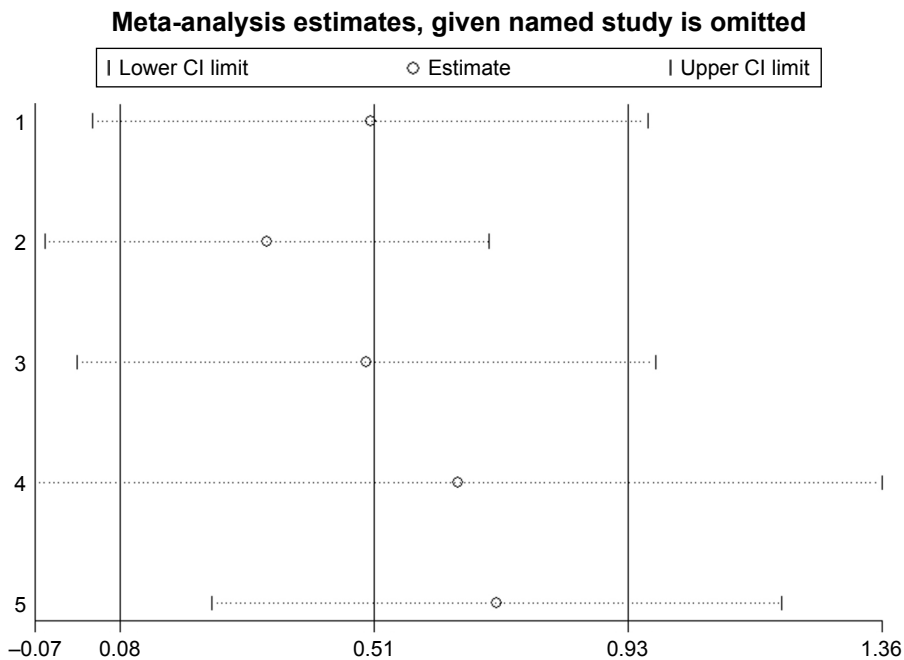
Meta-analysis estimates, given named study is omitted

Figure 7 The results of sensitivity analysis of the pooled HR for CSS.
Abbreviations: CSS, cancer-specific survival; HR, hazard ratio.

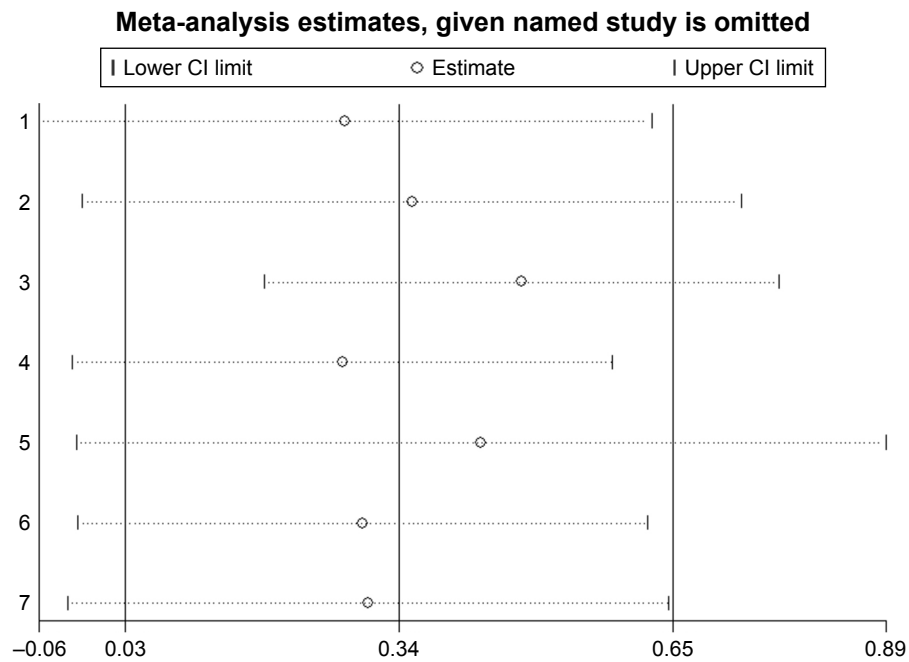**Meta-analysis estimates, given named study is omitted**

Figure 8 The results of sensitivity analysis of the pooled OR for postoperative 30dC.
Abbreviations: 30dC, 30-day complication; OR, odds ratio.

selection and data analysis. Second, all the included studies were published in English, which might lead to some language bias. Third, the cutoffs of high pretreatment serum albumin levels were not in consistency among the included studies. The value of 3.5 g/dL was defined as the cutoff value for evaluating serum albumin level in most of the included studies. However, it might be doubtful that 3.5 g/dL could act as an accurate cutoff value for evaluating the serum albumin level in BC patients, considering that the cutoff values for high serum albumin level were >3.5 g/dL in a few studies. Therefore, further high-quality clinical studies with large sample size are needed to determine a definite and efficient
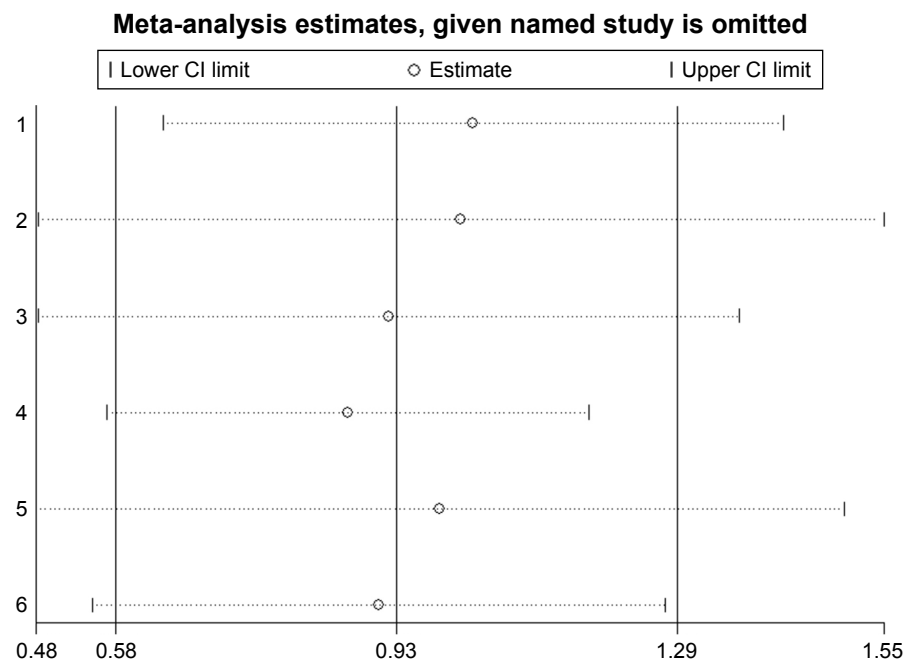
Meta-analysis estimates, given named study is omitted

Figure 9 The results of sensitivity analysis of the pooled OR for postoperative 90dM.
Abbreviations: 90dM, 90-day mortality; OR, odds ratio.

Table 3 Subgroup analysis of preoperative serum albumin and outcomes of BC patients

Variables	Outcome	Studies	Patients	HR (95% CI)	P-value	Model	Heterogeneity I² %	Erogeneity P-value
Ethnicity								
Asian	OS	4	1,655	1.37 (1.11–1.69)	<0.01	Fixed	0.0	0.61
	CSS	3	831	1.32 (0.81–2.14)	0.27	Random	65.2	0.06
Non-Asian	OS	4	1,919	2.35 (1.65–3.34)	<0.01	Random	58.4	0.06
	CSS	2	255	3.21 (0.65–15.80)	0.15	Random	86.2	<0.01
Analysis type								
Univariate	CSS	1	117	1.79 (0.73–4.37)	0.20	–	–	–
	90dM	5	7,426	2.42 (1.75–3.33)	<0.01	Fixed	31.5	0.21
	CSS	5	969	1.65 (1.03–2.63)	0.04	Random	89.7	<0.01
Multivariate	90dM	1	1,097	3.03 (1.31–7.02)	0.01	–	–	–
Cutoff value								
3.5 g/dL	CSS	2	412	1.12 (0.69–1.82)	0.66	Fixed	42.1	0.19
	30dC	4	7,915	1.74 (1.39–2.17)	<0.01	Fixed	13.4	0.33
	90dM	4	7,257	2.39 (1.54–3.73)	<0.01	Fixed	<0.01	0.12
Others	CSS	3	674	2.22 (1.18–4.17)	0.01	Random	72.7	0.03
	30dC	3	3,674	1.06 (0.61–1.83)	0.85	Random	84.3	<0.01
	90dM	2	1,266	2.66 (1.65–4.28)	<0.01	Fixed	0.0	0.71

Abbreviations: BC, bladder cancer; CSS, cancer-specific survival; 30dC, 30-day complication; 90dM, 90-day mortality; HR, hazard ratio; OS, overall survival.

cutoff value for judging the serum albumin level in BC patients before the findings of our study are widely applied to clinical practice. Fourth, the inconsistencies in the follow-up period and the baseline characteristics of patients also existed in this meta-analysis, and they may result in significant heterogeneities, consequently affecting the robustness of the combined analyses. Therefore, we wish to stress that the results of this meta-analysis should be cautiously interpreted, and further large-scale prospective clinical trials are urgently needed to confirm the impact of pretreatment serum albumin level on the outcomes of BC patients in the future.

Conclusion

This meta-analysis indicated that decreased pretreatment serum albumin level was correlated with worse survival and higher incidence of postoperative complication and mortality in patients with BC. Nevertheless, further high-quality trials with large sample size should be performed to confirm the results of this meta-analysis.

Disclosure

The authors report no conflicts of interest in this work.

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