Comprehensive evaluation of serum hepatic proteins in predicting prognosis among cancer patients with cachexia: an observational cohort study

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Abstract

Background Hepatic proteins, including albumin, prealbumin, and transferrin have been confirmed to be prognostic predictors in various cancers. This study aimed to comprehensively assess the prognostic value of these three serum markers in patients with cancer cachexia.

Methods This multicenter prospective cohort study included 1303 cancer cachexia patients, among whom 592 deaths occurred during a median follow-up of 20.23 months. The definition of cachexia was based on the 2011 international consensus. Concordance index (C-index) and receiver operating characteristic (ROC) curves were applied to compare the prognostic performance. The primary outcome was overall survival, which was calculated using the Kaplan–Meier method generated by log-rank test. A Cox proportional hazard regression model was used to identify independent predictors associated with survival. The secondary outcomes included 90-days mortality and quality of life (QoL).

Results C-index and ROC curves showed that albumin had the most accurate predictive capacity for survival, followed by transferrin and prealbumin. Multivariate Cox analysis confirmed that low albumin (hazard ratio [HR] = 1.51, 95% confidence interval [95%CI] = 1.28–1.80, $P < 0.001$), prealbumin (HR = 1.42, 95%CI = 1.19–1.69, $P < 0.001$), and transferrin (HR = 1.50, 95%CI = 1.25–1.80, $P < 0.001$) were independent risk factors for long-term survival in cancer patients with cachexia. In subgroup analysis, the prognostic value of low albumin was significant in patients with upper gastrointestinal, hepatobiliary and pancreatic, and colorectal cancers; low prealbumin was significant in colorectal cancer; and low transferrin was significant in patients with upper gastrointestinal and colorectal cancer. All three hepatic proteins were valuable as prognostic predictors for patients with advanced (Stage III and IV) cancer with cachexia. The risks of 90-days mortality and impaired QoL were higher in cachexia patients with low albumin, prealbumin, and transferrin levels.

Conclusion Low albumin, prealbumin, and transferrin levels were all independent prognostic factors affecting patients with cancer cachexia, especially in patients in the advanced stages. These results highlight the value

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of routinely checking serum hepatic proteins in clinical practice to predict the prognosis of patients with cancer cachexia.

Keywords Transferrin, Albumin, Prealbumin, Cachexia, Cancer, Prognosis

Introduction

Cancer-related cachexia is a very common and devastating syndrome, with an estimated prevalence of 50–80% ranging across cancer types [1]. Cachexia is highly associated with cancers of the pancreas, esophagus, gastric system, lung, liver, and bowel; this group of malignancies accounts for half of all cancer-related deaths worldwide [2]. As cachexia is a multifactorial disorder characterized by involuntary loss of skeletal muscle mass and systemic inflammation, it adversely affects patient quality of life (QoL), treatment response, and survival [3]. Notably, almost 30% cancer patients eventually die due to their extremely weakened state caused by cachexia [4]. Moreover, conventional nutritional supplementation alone cannot improve cachexia because of cancer-related metabolic alterations [5]. A spectrum of both tumor- and host-derived factors leads to hypercatabolism, muscle degradation, and acute phase response in cachexia patients [6]. The pathophysiology of cachexia is characterized by negative protein and energy balance. Therefore, serum proteins may serve as promising prognostic predictor for patients with cancer cachexia.

Malnutrition and systemic inflammation are two widely recognized hallmarks of cachexia [7]. The liver, a major organ affected by cachexia, produces fewer proteins both in a protein-deficient state and in the presence of cytokine-induced inflammatory disorders [8]. Albumin, prealbumin, and transferrin are three representative hepatic proteins that commonly used to identify prognosis for malnourished patients in the clinical practice [9]. In addition, albumin and transferrin are also negative acute-phase proteins, decreasing at least 25% during inflammatory conditions [10]. Albumin, which accounts for more than half of blood proteins, reflects the protein status of the blood and internal organs [11]. It can also modulate the inflammatory reaction through several physiological functions, including antioxidant activity, binding to inflammatory mediators, regulation of leukocyte migration and maintenance of vascular integrity [12]. Prealbumin has a shorter half-life of 2 days in plasma; and has been recognized as a more sensitive indicator of nutritional status than albumin [13]. Of note, Dennis et al. also reported that inflammation or changes in inflammation appeared to exert a much more-powerful influence on prealbumin concentration [14]. Accumulating studies also confirmed that transferrin serves as an effective index of nutritional and inflammatory status

[14, 15]. Therefore, our study hypothesized that these three hepatic proteins, reflecting nutritional and inflammatory status, may be promising prognostic predictor for patients with cachexia.

Serum albumin level serves as a key factor in defining cancer cachexia and cancer-related malnutrition. Results from a previous study also showed that serum albumin and prealbumin levels were lower in patients with cancer cachexia [16]. The prognostic value of low albumin levels has been confirmed in cancer patients with cachexia [17]. Prealbumin was considered as an independent risk factor for survival in patients with liver cancer [18] and resected esophageal squamous cell cancer [19]. A recent study also reported that serum transferrin and prealbumin may outperform albumin in identifying patients with esophageal cancer with malnutrition and poor prognosis [20]. However, no previous study has systemically investigated the prognostic value of these three serum nutritional markers in patients with cancer cachexia. In addition, quality of life (QoL) is an important person-cantered assessment in both clinical practice and research that needs to be addressed [21]. Patients with cancer cachexia are encountered with impaired QoL and increasing symptom burden [22]. The systemic study on association between hepatic proteins with QoL in patients with cancer cachexia is still lacking. Therefore, our study aimed to thoroughly investigate and compare the value of albumin, prealbumin and transferrin in predicting survival and QoL in patients with cancer cachexia.

Patients and methods

Study population and design

This multicenter prospective cohort study extracted data from the Investigation on Nutrition Status and its Clinical Outcomes of Common Cancers (INSCOC) project of China (registration number: ChiCTR1800020329) [23]. A total of 22,783 patients pathologically diagnosed with cancer from 47 clinical centers were enrolled in this study from 2013 to 2020. The exclusion criteria were as follows: a) presence of clinically evident active infection or severe systemic immunodeficiency disease, b) important variables required for analysis in the study were lacking, and c) a hospital stay of less than 48 h. Eventually, 4091 patients were eligible for the initial analysis, of which 1303 were diagnosed with cachexia based on the 2011 international consensus definition of cachexia (Fig. S1). The definition of cancer cachexia was as follows [3]: (1) a weight

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loss > 5% over the past 6 months (in the absence of simple starvation); (2) body mass index [BMI] < 20 and any degree of weight loss > 2%; or (3) appendicular skeletal muscle index consistent with sarcopenia and any degree of weight loss > 2%. The assessment of skeletal muscle depletion was performed by mid–upper arm muscle area anthropometry (men < 32 cm^2, women < 18 cm^2). This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and was approved by the ethics committees of all participating institutions. Written informed consent was obtained from all the participants prior to their participation.

Baseline characteristics

We trained personnel to collect baseline characteristics, including clinical information (sex, age, alcohol consumption, smoking status, diabetes, hypertension, type of cancer, tumor/node/metastasis (TNM) stage, treatment (e.g., surgery, chemotherapy, and radiotherapy), functionality, anthropometric data, laboratory data, and QoL. The data from the first investigation before anti-cancer treatment was analyzed for patients. The following tumor types were included: lung, upper gastrointestinal, hepatobiliary and pancreatic, colorectal, urogenital (endometrial, cervical, bladder, prostate, and ovarian), and other cancers. All pathological staging was defined according to the eighth edition of the American Joint Committee on Cancer TNM staging system. The Eastern Cooperative Oncology Group performance status (ECOG-PS) was performed to assess patients' functionality. Anthropometric data included BMI, hand grip strength [HGS], and calf circumference [CC]. BMI was calculated as the weight in kilograms divided by the height in meters squared (kg/m^2). HGS was measured in the nondominant hand using an electronic handgrip dynamometer. The patients were placed in the supine position with 90° of knee flexion to measure the CC.

Outcomes of present study

To collect data on clinical outcomes, telephone follow-up surveys, periodical reexaminations, and readmissions were provided to all patients. The primary outcome of our study was overall survival, which was defined as the interval between the first assessment in the clinic until the date of death, the date of withdrawal from the study, the end of follow-up (October 30th, 2020), or the time of the last contact, whichever came first. The secondary outcomes were short-term outcomes and QoL. The short-term survival refers to the outcome of the patient within three months of treatment. All patients filled in the 30-item European Organization for Research and Treatment of Cancer QoL Questionnaire, version 3.0 within 48h after first admission for QoL assessment.

This questionnaire consists of five multi-item functional scales (physical, role, social, emotional, and cognitive function), three multi-item symptom scales (fatigue, pain, and nausea and vomiting), six single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact), and a two-item global QoL scale [24]. The 30-item Cancer QoL Questionnaire summary score was calculated as follows: summary score = (physical functioning + role functioning + social functioning + emotional functioning + cognitive functioning + (100-fatigue) + (100-pain) + (100-nausea & vomiting) + (100-dyspnea) + (100-insomnia) + (100-appetite loss) + (100-constipation) + (100-diarrhea))/13 [25].

Statistical analysis

Statistical analyses were performed using R software version 3.6.2. Continuous variables are expressed as median (interquartile range) and compared using the Mann-Whitney U test. Categorical variables are expressed as absolute numbers or percentages and compared using the χ2 test or Fisher's exact test. Correlations between the two variables were analyzed using Pearson's correlation coefficient. Concordance index (C-index) and receiver operating characteristic (ROC) curves were applied to assess the predictive value of the indicator. The dose-response relationship between serum proteins and survival was evaluated using restricted cubic regression with three knots. We used an outcome-oriented method to set optimal cutoff points for continuous variables, which can maximize the log-rank statistics. Overall survival was calculated and compared using the Kaplan–Meier method generated by the log-rank test. Univariate and multivariate Cox regression analyses were performed to identify independent predictors associated with poor OS, using hazard ratios (HRs) and 95% confidence intervals (95%CIs). Poisson generalized linear model was used to assess the association between the serum markers and QoL. Single variable significance was set at $P < 0.05$ in the univariate analyses. Significant variables were entered into the multivariate competing-risks regression models. Interaction terms were used to investigate whether there was any association between the main variables and the other clinical parameters. Statistical significance was defined as a two-tailed *P*-value < 0.05.
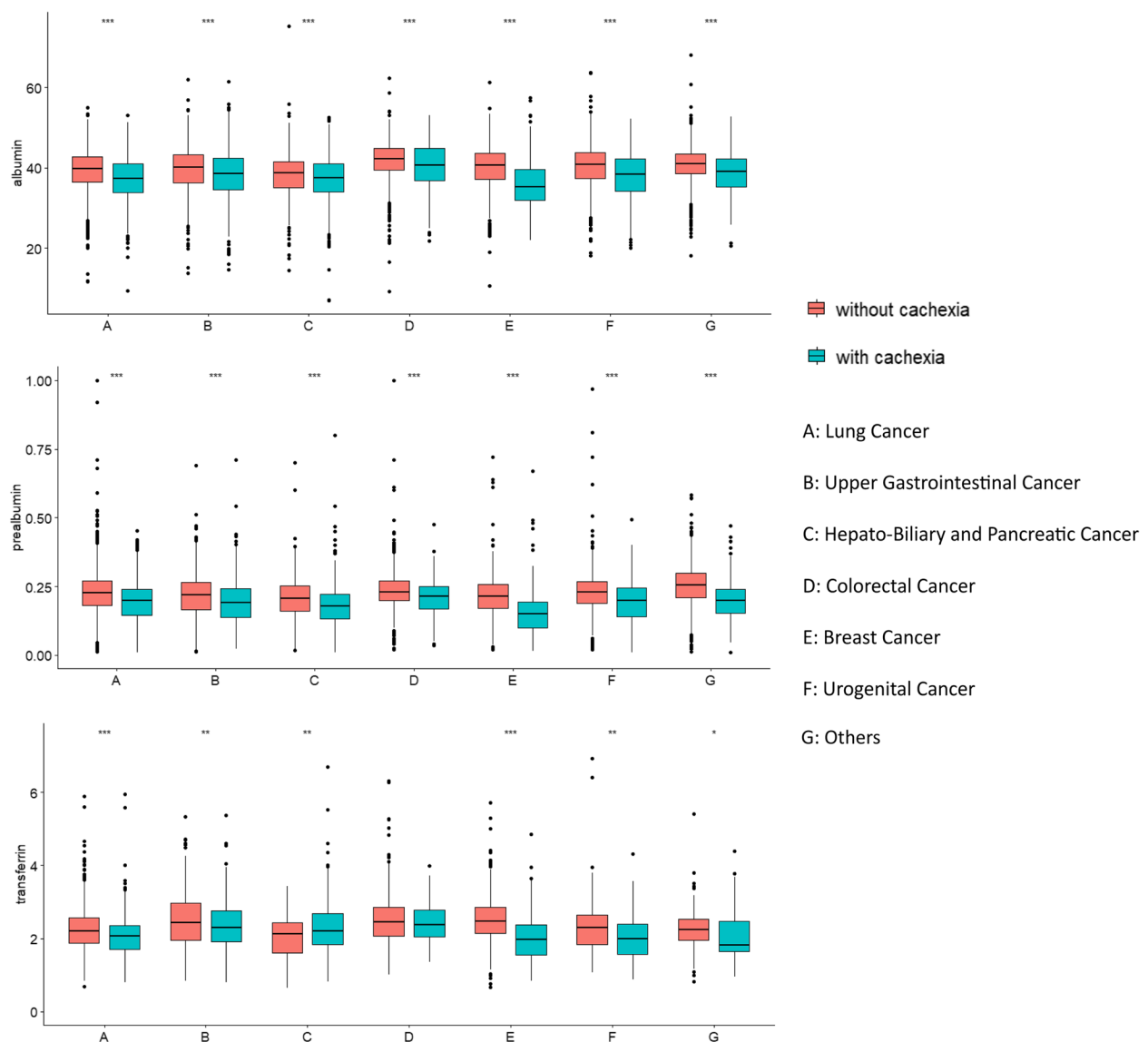
Results

Clinical characteristics

A total of 4091 cancer patients were analyzed in the first step, among which 1303 were diagnosed with cachexia based on the 2011 international consensus of cachexia. The median age of patients with cachexia was 60 years (IQR [53.00–66.00]), and the proportion of males and females was 59.6% and 40.4%, respectively. The most

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frequent tumors were upper gastrointestinal tract (29.2%), lung (27.8%), colorectal (19.2%), hepatobiliary and pancreatic (8.6%), and breast (4.8%). Ninety-six patients (7.4%) had stage I cancer, 211 (16.2%) had stage II, 386 (29.6%) had stage III, and 610 (46.8%) had stage IV cancer. Cancer cachexia patients were more likely to be male, older, have a history of smoking and drinking, have advanced tumor stage, ECOG grade > 1, lower BMI, calf circumference and hand grip strength, increased NLR, and decreased albumin, prealbumin, and transferrin levels. A box plot was created to compare the

levels of the three serum markers between patients with and without cachexia in different tumor types (Fig. 1). Detailed demographic information, tumor-related characteristics, and laboratory data are presented in Table 1. There was a moderate positive correlation between albumin and transferrin (male: $R = 0.46$, $P < 0.001$; female: $R = 0.38$, $P < 0.001$) and prealbumin (male: $R = 0.44$, $P < 0.001$; female: $R = 0.42$, $P < 0.001$) levels. A weak positive correlation was observed between prealbumin and transferrin levels (male: $R = 0.33$, $P < 0.001$; female: $R = 0.20$, $P < 0.001$) (Fig. S2).

A: Lung Cancer

B: Upper Gastrointestinal Cancer

C: Hepato-Biliary and Pancreatic Cancer

D: Colorectal Cancer

E: Breast Cancer

F: Urogenital Cancer

G: Others

Fig. 1 The levels of three serum nutritional markers in cancer patients with or without cachexia (ns *P*-value > 0.05, **P-value < 0.05, ***P-value < 0.01, ****P-value < 0.001)

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Table 1 Patients baseline characteristics

Variables	All patients (*n* = 4091)	Cachexia patients (*n* = 1303)	Non-cachexia patients (*n* = 2788)	*P* value
Age, years	59.00 (51.00–65.00)	60.00 (53.00–66.00)	59.00 (50.00–65.00)	< 0.001
Gender (Male/Female)	2184/1907 (53.4%/46.6%)	777/526 (59.6%/40.4%)	1407/1381 (50.5%/49.5%)	< 0.001
Diabetes (Yes/No)	351/3740 (8.6%/91.4%)	110/1193 (8.4%/91.6%)	241/2547 (8.6%/91.4%)	0.877
Hypertension (Yes/No)	732/3359 (17.9%/82.1%)	234/1069 (18.0%/82.0%)	498/2290 (17.9%/82.1%)	0.975
Smoking (Yes/No)	1714/2377 (41.9%/58.1%)	600/703 (46.0%/54.0%)	1114/1674 (40.0%/60.0%)	< 0.001
Drinking (Yes/No)	898/3193 (22.0%/78.0%)	333/970 (25.6%/74.4%)	565/2223 (20.3%/79.7%)	< 0.001
Type of cancer				< 0.001
Lung	1370 (33.5%)	362 (27.8%)	1008 (36.2%)	
Upper gastrointestinal	752 (18.4%)	381 (29.2%)	371 (13.3%)	
Hepatobiliary and pancreatic	181 (4.4%)	112 (8.6%)	69 (2.5%)	
Colorectal	634 (15.5%)	250 (19.2%)	384 (13.8%)	
Breast	690 (16.9%)	63 (4.8%)	627 (22.5%)	
Others	464 (11.3%)	135 (10.4%)	329 (11.8%)	
TNM stages				< 0.001
I	417 (10.2%)	96 (7.4%)	321 (11.5%)	
II	842 (20.6%)	211 (16.2%)	631 (22.6%)	
III	1151 (28.1%)	386 (29.6%)	765 (27.4%)	
IV	1681 (41.1%)	610 (46.8%)	1071 (38.4%)	
Surgery (Yes/No)	2021/2070 (49.4%/50.6%)	647/656 (49.7%/50.3%)	1374/1414 (49.3%/50.7%)	0.851
Radiotherapy (Yes/No)	507/3584 (12.4%/87.6%)	149/1154 (11.4%/88.6%)	358/2430 (12.8%/87.2%)	0.222
Chemotherapy (Yes/No)	2516/1575 (61.5%/38.5%)	731/572 (56.1%/43.9%)	1785/1003 (64.0%/36.0%)	< 0.001
ECOG grade (≤ 1/> 1)	2063/2028 (50.4%/49.6%)	526/777 (40.4%/59.6%)	1537/1251 (55.1%/44.9%)	< 0.001
Body mass index, kg/m^2	22.58 (20.20–24.82)	20.40 (18.55–22.89)	23.37 (21.23–25.46)	< 0.001
Calf circumference, cm	33.50 (31.00–36.00)	32.00 (30.00–34.35)	34.00 (32.00–36.50)	< 0.001
Hand grip strength, kg	24.80 (19.00–31.07)	23.60 (18.00–30.15)	25.15 (19.60–31.60)	< 0.001
Neutrophil to lymphocyte ratio (NLR)	2.36 (1.58–3.75)	2.74 (1.68–4.60)	2.24 (1.54–3.42)	< 0.001
Albumin, g/L	40.00 (36.60–42.90)	38.60 (34.90–42.10)	40.50 (37.40–43.40)	< 0.001
Prealbumin, g/L	0.22 (0.17–0.26)	0.20 (0.15–0.24)	0.23 (0.18–0.27)	< 0.001
Transferrin, g/L	2.27 (1.89–2.67)	2.13 (1.75–2.54)	2.33 (1.96–2.73)	< 0.001

Abbreviations: *TNM* Tumor/node/metastasis, *ECOG* Eastern Cooperative Oncology Group

## Comparison between albumin, prealbumin and transferrin in predicting survival

During a median follow-up of 20.23 months, we recorded a total of 592 deaths in patients with cancer cachexia. The C-index for OS was the highest for albumin (0.608, IQR [0.584–0.633]), followed by transferrin (0.595, IQR [0.571–0.619]) and prealbumin (0.572, IQR [0.546–0.597]) (Table S1). The time-dependent ROC curve showed a similar trend: the 1-year AUC of albumin, transferrin, and prealbumin were 0.650, 0.633, and 0.600, respectively; and the 3-year AUC of albumin, transferrin, and prealbumin were 0.615, 0.598, and 0.571, respectively (Fig. 2). Restricted cubic spline plots showed an association between serum nutritional markers with the HR for all-cause mortality in cancer patients with cachexia (Fig. 3). The risk of cancer-related mortality increased as serum albumin, prealbumin and transferrin levels decreased. The optimal cutoff value of albumin,

prealbumin, and transferrin for cancer cachexia patients in our study was 38.7 g/L, 0.17 g/L, and 2.29 g/L, respectively, as calculated by standardized log-rank statistics (Fig. S3).

Survival analysis of albumin, prealbumin, and transferrin in cancer cachexia patients

Kaplan–Meier curves showed that patients in the low albumin, prealbumin, and transferrin groups had markedly poorer prognoses than those in the high serum marker group (Fig. 4). After adjusting for age, sex, smoking, drinking, BMI, HGS, CC, tumor type, tumor stage, surgery, chemotherapy, ECOG grade, and NLR, multivariate Cox proportional risk regression analysis showed that low albumin (HR = 1.51, 95%CI = 1.28–1.80, *P* < 0.001), prealbumin (HR = 1.42, 95%CI = 1.19–1.69, *P* < 0.001), and transferrin (HR = 1.50, 95%CI = 1.25–1.80, *P* < 0.001) were independent risk factors for prognosis
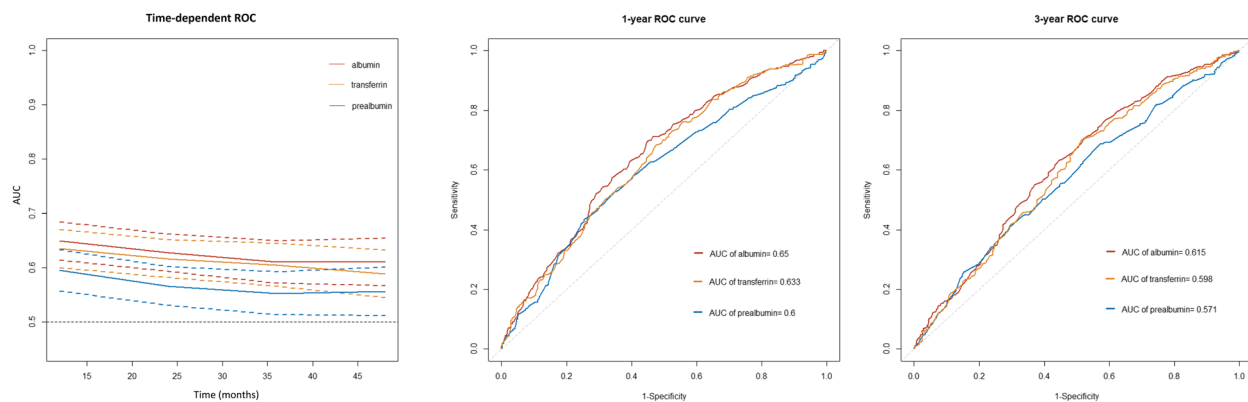
Fig. 2 ROC curves of albumin, prealbumin and transferrin. Abbreviation: ROC, receiver operating characteristic; AUC, area under curve

(Table 2). We also performed two sensitivity analyses to confirm the prognostic value in patients with cachexia (Fig. S4). First, we excluded 88 patients with liver diseases such as chronic hepatitis, cirrhosis, and liver cancer. Low albumin (adjusted HR = 1.55, 95%CI [1.30 – 1.85], $P < 0.001$), prealbumin (adjusted HR = 1.41, 95%CI [1.18–1.69], $P < 0.001$), and transferrin (adjusted HR = 1.53, 95%CI [1.27–1.84], $P < 0.001$) levels were still associated with shorter OS and were independently unfavorable factors for prognosis. Secondly, 175 patients who died within 6 months after the beginning of this study were also excluded, the overall result was unchanged, with adjusted HR of albumin, prealbumin and transferrin of 1.38 (95%CI [1.13–1.69], $P = 0.001$), 1.32 (95%CI [1.07–1.63], $P = 0.00–9$) and 1.44 (95%CI [1.17–1.77], $P < 0.001$).

Subgroup analysis

We performed subgroup analyses based on various clinicopathological characteristics including age, sex, tumor type, TNM stage and ECOG grade (Fig. 5). Low albumin and prealbumin levels were independent risk factors for survival in all age, sex, and ECOG grade groups. However, the prognostic performance of transferrin in patients aged 65 years was not statistically significant. Low albumin levels were associated with high-risk mortality in patients with upper gastrointestinal cancer, hepatobiliary and pancreatic cancer, and colorectal cancer. The predictive ability of low prealbumin levels for survival was significant in patients with colorectal cancer. Low transferrin levels were confirmed as a prognostic predictor in patients with upper gastrointestinal cancer and colorectal cancer. Notably, the prognostic value of the three serum markers was significant in patients with advanced TNM stage (stage III and IV).

Association between serum hepatic proteins with secondary outcomes

There were 83 cancer patients with cachexia died within 90 days after joining this study. We performed multivariate Cox regression analysis to investigate the impact of serum markers on short-term survival. As the value of albumin and transferrin decreased per standard deviation, the risk of mortality within 90 days rose to 1.60 (95%CI = 1.34–1.92, $P < 0.001$) and 1.37 (95%CI = 1.07–1.76, $P = 0.031$) times, respectively, after adjusting for confounding factors (Table 2). When classified by cut-off value, we found that low albumin (HR = 3.46, 95%CI = 2.01–5.95, $P < 0.001$) and transferrin (HR = 1.78, 95%CI = 1.05–3.02, $P = 0.031$) also served as independent risk factors for short-term survival. A similar trend was observed for prealbumin; however, it was not statistically significant. In addition, patients with low levels of serum hepatic proteins were more likely to have impaired QoL (Table S2). Of note, prealbumin had an effective stratification value in each domain of the QLQ-C3 in patients with cancer cachexia. In Poisson generalized linear model, we found that low albumin, transferrin and prealbumin levels were independent factors negatively associated with QoL (Table 3).

Discussion

Malnutrition and systemic inflammation have been recognized for decades as predictors of survival in patients with cancer. Serum hepatic proteins, easily quantified biomarkers, are widely used to assess nutritional risk and reflect inflammatory status in clinical practice. As a result, a number of previous studies have explored the prognostic value of serum hepatic proteins in cancer patients. Serum albumin has been described as an independent unfavorable factor for survival in patients with lung, gastric, colorectal, pancreatic, and breast cancer
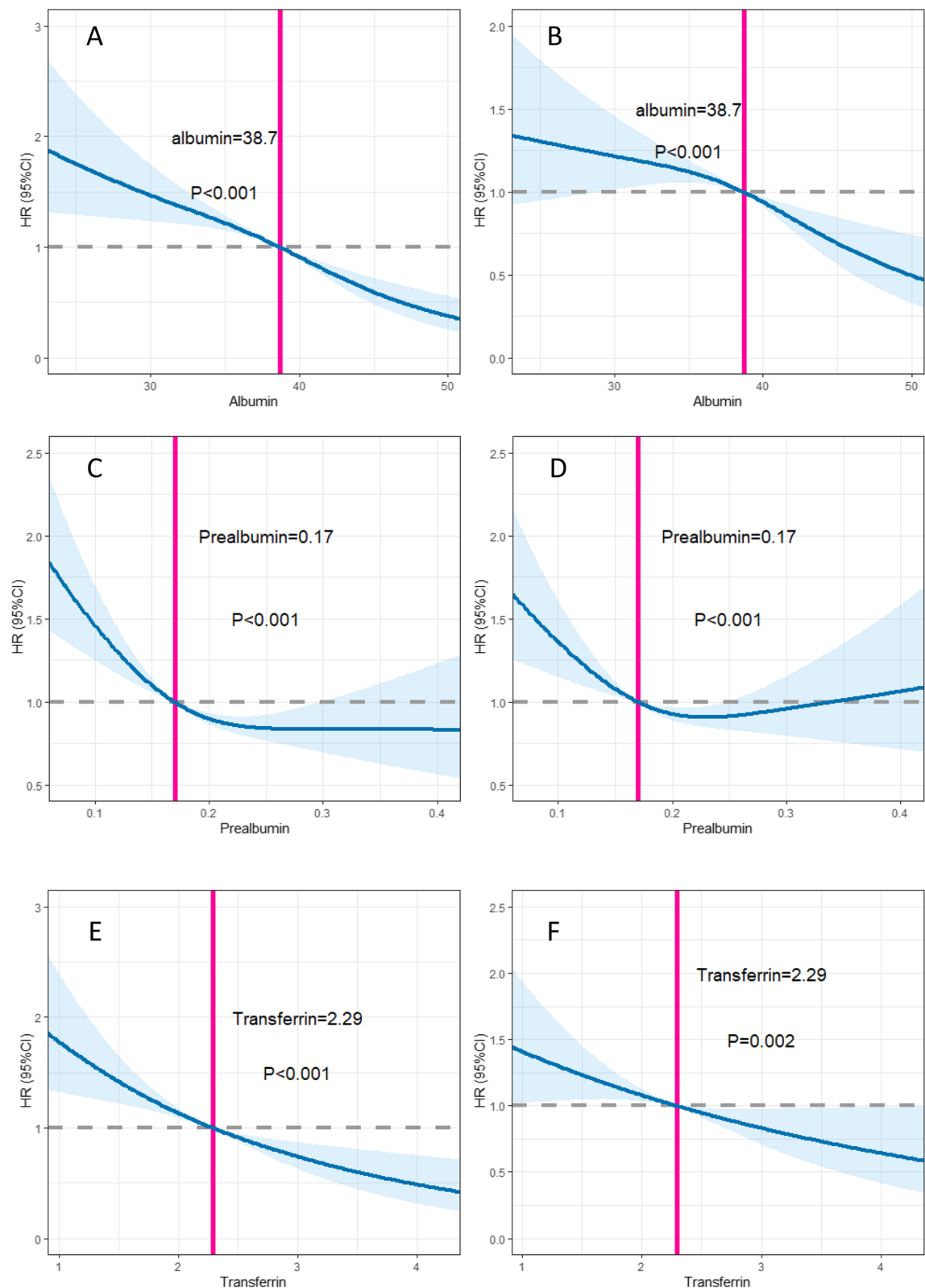
Fig. 3 Restricted Cubic spline plot shows relation between nutritional markers and all-cause mortality. Abbreviation: HR, hazard ratio. **A**, **C**, **E** Unadjusted model; **B**, **D**, **F** Adjusted for age, sex, smoking, drinking, diabetes, hypertension, tumor type, TNM stage, treatments, ECOG, BMI, HGS, CC and NLR

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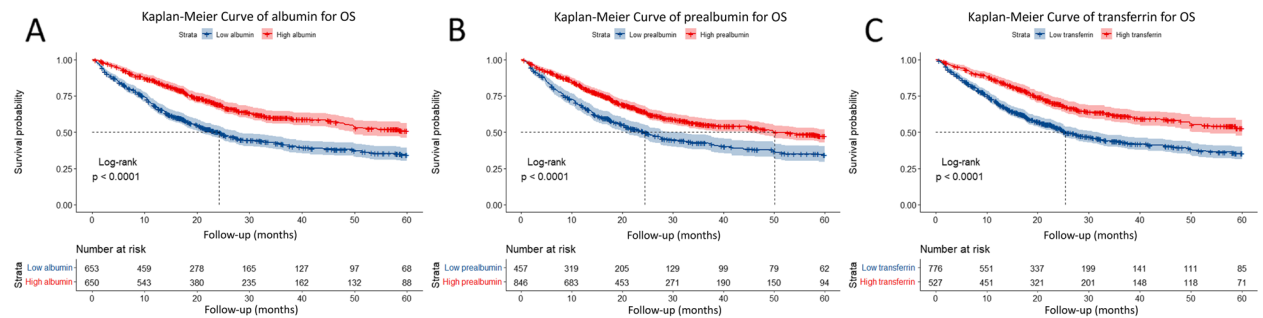
Fig. 4 Kaplan-Meier curves for OS in cancer cachexia patients

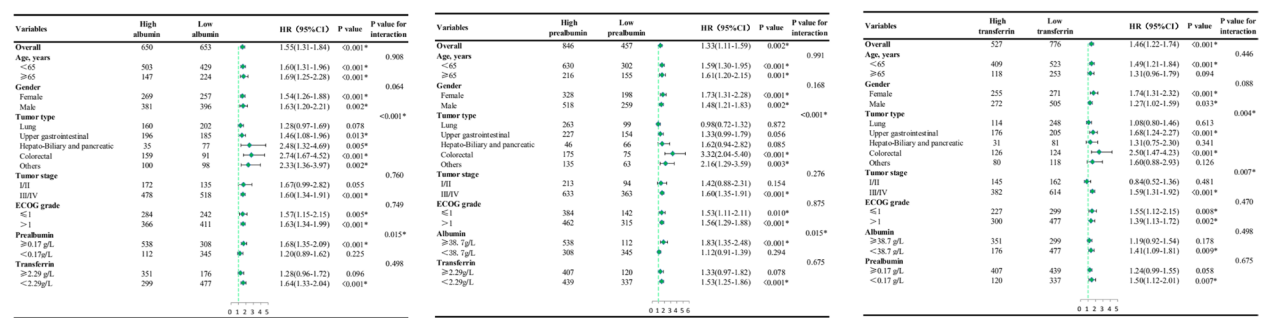**Table 2** Cox proportional hazard regression analyses of albumin, prealbumin and transferrin

Groups	No. of patients	Crude model		Adjusted Model[a]		Adjusted Model[b]	
		HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Long-term Survival							
Albumin							
By per SD		1.33 (1.23–1.43)	< 0.001	1.23 (1.14–1.33)	< 0.001	1.19 (1.10–1.29)	< 0.001
≥ 38.7 g/L	650	Reference		Reference		Reference	
< 38.7 g/L	653	1.82 (1.55–2.15)	< 0.001	1.57 (1.32–1.86)	< 0.001	1.51 (1.28–1.80)	< 0.001
Prealbumin							
By per SD		1.20 (1.10–1.30)	< 0.001	1.16 (1.07–1.26)	< 0.001	1.12 (1.03–1.23)	0.008
≥ 0.17 g/L	846	Reference		Reference		Reference	
< 0.17 g/L	457	1.57 (1.33–1.84)	< 0.001	1.39 (1.18–1.65)	< 0.001	1.42 (1.19–1.69)	< 0.001
Transferrin							
By per SD		1.31 (1.20–1.43)	< 0.001	1.18 (1.08–1.29)	< 0.001	1.18 (1.08–1.29)	< 0.001
≥ 2.29 g/L	527	Reference		Reference		Reference	
< 2.29 g/L	776	1.78 (1.49–2.11)	< 0.001	1.52 (1.27–1.81)	< 0.001	1.50 (1.25–1.80)	< 0.001
Short-term Survival (90 days)							
Albumin							
By per SD		1.79 (1.51–2.12)	< 0.001	1.74 (1.46–2.08)	< 0.001	1.60 (1.34–1.92)	< 0.001
≥ 38.7 g/L	650	Reference		Reference		Reference	
< 38.7 g/L	653	4.00 (2.35–6.82)	< 0.001	3.90 (2.27–6.72)	< 0.001	3.46 (2.01–5.95)	< 0.001
Prealbumin							
By per SD		1.18 (0.94–1.47)	0.153	1.16 (0.92–1.44)	0.206	1.03 (0.83–1.28)	0.783
≥ 0.17 g/L	846	Reference		Reference		Reference	
< 0.17 g/L	457	1.84 (1.20–2.83)	0.005	1.74 (1.11–2.72)	0.015	1.34 (0.84–2.14)	0.212
Transferrin							
By per SD		1.59 (1.25–2.03)	< 0.001	3.67 (1.59–8.44)	0.001	1.37 (1.07–1.76)	0.013
≥ 2.29 g/L	527	Reference		Reference		Reference	
< 2.29 g/L	776	2.19 (1.32–3.61)	0.002	1.52 (1.27–1.81)	< 0.001	1.78 (1.05–3.02)	0.031

During a median follow-up of 20.23 months, 592 deaths were recorded

Abbreviations: *HR* Hazard ratio, *CI* Confidence interval, *SD* Standard deviation

[a] Adjusted for age, sex, tumor type and TNM stage

[b] Adjusted for variables found significant at *P* < 0.05 in the univariate analyses, including age, sex, drinking, smoking, tumor type, TNM stage, surgery, radiotherapy, chemotherapy, ECOG, BMI, HGS, CC and NLR

[26]. Some studies have also combined albumin with other parameters to predict the prognosis of patients with cancer. The prognostic nutritional index (PNI), calculated using albumin and lymphocyte counts in the serum, is an effective prognostic factor for various malignancies, especially digestive system carcinomas [27].

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Albumin subgroup

Variables	High albumin	Low albumin	HR (95%CI)	P value	P value for interaction
Overall	650	653	1.55(1.31-1.84)	<0.001*	
Age, years					0.908
<65	503	429	1.60(1.31-1.96)	<0.001*	
≥65	147	224	1.69(1.25-2.28)	<0.001*	
Gender					0.064
Female	269	257	1.54(1.26-1.88)	<0.001*	
Male	381	396	1.63(1.20-2.21)	0.002*	
Tumor type					<0.001*
Lung	160	202	1.28(0.97-1.69)	0.078	
Upper gastrointestinal	196	185	1.46(1.08-1.96)	0.013*	
Hepato-Biliary and pancreatic	35	77	2.48(1.32-4.69)	0.005*	
Colorectal	159	91	2.74(1.67-4.52)	<0.001*	
Others	100	98	2.33(1.36-3.97)	0.002*	
Tumor stage					0.760
I/II	172	135	1.67(0.99-2.82)	0.055	
III/IV	478	518	1.60(1.34-1.91)	<0.001*	
ECOG grade					0.749
≤1	284	242	1.57(1.15-2.15)	0.005*	
>1	366	411	1.63(1.34-1.99)	<0.001*	
Prealbumin					0.015*
≥0.17 g/L	538	308	1.68(1.35-2.09)	<0.001*	
<0.17g/L	112	345	1.20(0.89-1.62)	0.225	
Transferrin					0.498
≥2.29 g/L	351	176	1.28(0.96-1.72)	0.096	
<2.29g/L	299	477	1.64(1.33-2.04)	<0.001*	

Prealbumin subgroup

Variables	High prealbumin	Low prealbumin	HR (95%CI)	P value	P value for interaction
Overall	846	457	1.33(1.11-1.59)	0.002*	
Age, years					0.991
<65	630	302	1.59(1.30-1.95)	<0.001*	
≥65	216	155	1.61(1.20-2.15)	0.001*	
Gender					0.168
Female	328	198	1.73(1.31-2.28)	<0.001*	
Male	518	259	1.48(1.21-1.83)	0.002*	
Tumor type					<0.001*
Lung	263	99	0.98(0.72-1.32)	0.872	
Upper gastrointestinal	227	154	1.33(0.99-1.79)	0.056	
Hepato-Biliary and pancreatic	46	66	1.62(0.94-2.82)	0.085	
Colorectal	175	75	3.32(2.04-5.40)	<0.001*	
Others	135	63	2.16(1.29-3.59)	0.003*	
Tumor stage					0.276
I/II	213	94	1.42(0.88-2.31)	0.154	
III/IV	633	363	1.60(1.35-1.91)	<0.001*	
ECOG grade					0.875
≤1	384	142	1.53(1.11-2.11)	0.010*	
>1	462	315	1.56(1.29-1.88)	<0.001*	
Albumin					0.015*
≥38.7g/L	538	112	1.83(1.35-2.48)	<0.001*	
<38.7g/L	308	345	1.12(0.91-1.39)	0.294	
Transferrin					0.675
≥2.29g/L	407	120	1.33(0.97-1.82)	0.078	
<2.29g/L	439	337	1.53(1.25-1.86)	<0.001*	

Transferrin subgroup

Variables	High transferrin	Low transferrin	HR (95%CI)	P value	P value for interaction
Overall	527	776	1.46(1.22-1.74)	<0.001*	
Age, years					0.446
<65	409	523	1.49(1.21-1.84)	<0.001*	
≥65	118	253	1.31(0.96-1.79)	0.094	
Gender					0.088
Female	255	271	1.74(1.31-2.32)	<0.001*	
Male	272	505	1.27(1.02-1.59)	0.033*	
Tumor type					0.004*
Lung	114	248	1.08(0.80-1.46)	0.613	
Upper gastrointestinal	176	205	1.68(1.24-2.27)	<0.001*	
Hepato-Biliary and pancreatic	31	81	1.31(0.75-2.30)	0.341	
Colorectal	126	124	2.50(1.47-4.23)	<0.001*	
Others	80	118	1.60(0.88-2.93)	0.126	
Tumor stage					0.007*
I/II	145	162	0.84(0.52-1.36)	0.481	
III/IV	382	614	1.59(1.31-1.92)	<0.001*	
ECOG grade					0.470
≤1	227	299	1.55(1.12-2.15)	0.008*	
>1	300	477	1.39(1.13-1.72)	0.002*	
Prealbumin					0.498
≥0.17 g/L	407	439	1.24(0.99-1.55)	0.058	
<0.17 g/L	120	337	1.50(1.12-2.01)	0.007*	

Fig. 5 Subgroup analyses by potential modified factors. Abbreviation: CI, confidence interval; EOCG, Eastern Cooperative Oncology Group performance status. Note: During a median follow-up of 20.23 months, 592 deaths were recorded. Adjust for independent risk factors in multivariate Cox regression. Albumin: adjusting for smoking, tumor type, tumor stage, surgery, chemotherapy, ECOG grade and NLR; Prealbumin: adjusting for age, smoking, tumor type, tumor stage, surgery, chemotherapy, ECOG grade; Transferrin: adjusting for age, smoking, tumor type, tumor stage, surgery, chemotherapy, ECOG grade and NLR

Table 3 Generalized linear model analyses of nutritional marker associated with QoL

Groups	No. of patients	Crude model		Adjusted Model[a]		Adjusted Model[b]	
		Coefficients	*P*-value	Coefficients	*P*-value	Coefficients	*P*-value
Albumin							
By per SD		0.028	<0.001	0.021	<0.001	0.019	<0.001
≥38.7 g/L	650	Reference		Reference		Reference	
<38.7 g/L	653	-0.051	<0.001	-0.041	<0.001	-0.031	<0.001
Prealbumin							
By per SD		0.022	<0.001	0.019	<0.001	0.011	<0.001
≥0.17 g/L	846	Reference		Reference		Reference	
<0.17 g/L	457	-0.070	<0.001	-0.067	<0.001	-0.035	<0.001
Transferrin							
By per SD		0.021	<0.001	0.016	<0.001	0.013	<0.001
≥2.29 g/L	527	Reference		Reference		Reference	
<2.29 g/L	776	-0.030	<0.001	-0.021	0.001	-0.014	0.035

Abbreviations: *QoL* Quality of life, *SD* Standard deviation

[a] Adjusted for age, sex, tumor type and TNM stage

[b] Adjusted for age, sex, drinking, smoking, tumor type, TNM stage, surgery, radiotherapy, chemotherapy, ECOG

Accumulating studies have also confirmed that prealbumin and transferrin were effective for survival prediction in patients with cancer, even with a better performance than albumin [18–20]. However, research on serum hepatic proteins in the cancer cachexia population is lacking. The present study, comprehensively assessed the association between albumin, prealbumin, and transferrin levels and prognosis in cancer cachexia patients for the first time.

Consistently with previous studies, our results showed that cachexia patients have a lower level of serum hepatic protein than general cancer patients. This may be because several alterations were observed in the liver of patient with cachexia. In addition to muscle and adipose tissues, cachexia also affects other major organs, including liver protein synthesis [28]. Excessive amino acids resulting from muscle protein degradation result in an acute phase response (APR) and energy wasting in the liver [29]. Cachexia progression can also result in collagen deposition and fibrosis [30]. Poor protein-energy intake, impaired liver synthetic function, and inflammatory status result in low circulating hepatic protein levels among patients with cachexia [31]. Thus, the present study specifically set optimal cutoff values of albumin, prealbumin and transferrin for cancer cachexia population determined by standardized log-rank statistics, with figures of 38.7, 0.17, and 2.29 g/L respectively. Kaplan-Meier curves showed that patients with low serum hepatic protein levels had an obviously shorter OS time than those with high levels. In multivariate Cox analysis, we found that the

risks of reduced long-term survival in cancer cachexia patients with low albumin, prealbumin and transferrin levels were 1.51, 1.42, and 1.50 times higher than those with high hepatic protein levels. Of note, the prognostic value was independent from age, sex, drinking, smoking, tumor type, TNM stage, surgery, chemotherapy, ECOG, BMI, HGS, CC, and NLR. The results were unchanged in two sensitive analyses, with one excluding patients with liver disorders and the other excluding patients who died within six months of the beginning of our study.

Chiang et al. recently reported that the AUC value for diagnosing malnutrition was largest for prealbumin, followed by transferrin and albumin, with optimal breakpoints of 0.21, 2.06, and 43.0 g/L, respectively, for diagnosing malnutrition in esophageal cancer [20]. Milano et al. also showed that prealbumin was the most sensitive indicator of nutrition, and its levels and rates of change had prognostic significance in cancer of the large bowel [32]. These results are in accordance with the hallmarks of prealbumin levels. With its much shorter half-life, prealbumin is a more sensitive indicator of nutritional status than albumin [13]. However, the current study found the opposite result for predicting survival in patients with cancer cachexia: albumin had the most accurate prognostic value, followed by transferrin and prealbumin. The Nutrition Area of the Spanish Society of Endocrinology and Nutrition (SEEN) also states that albumin remains the strongest marker for long-term nutrition-related prognosis, especially mortality, although prealbumin has a reasonably good value for long-term mortality up to three years [33]. We speculate that prealbumin may outperform albumin in assessing nutritional status, but its prognostic performance in cancer cachexia patients is not as accurate as that of albumin. Routine checking of all three markers will help comprehensively reflect nutritional risk, predict survival, and provide timely intervention.

The development of cancer cachexia differs according to tumor site, TNM stage, and individual conditions [34]. Therefore, we performed subgroup analyses based on clinical variables including age, sex, tumor type, TNM stage, and ECOG grade. All three hepatic proteins were promising predictors of survival in patients with advanced TNM stages. This may be because advanced patients often have a worse nutritional status due to reduced food intake and increased energy consumption. A low albumin level is an independent unfavorable factor for cachexia patients with upper gastrointestinal, hepatobiliary and pancreatic and colorectal cancers. The prognostic value of transferrin has been observed in upper gastrointestinal and colorectal cancer. Low prealbumin levels only have prognostic discrimination performance in patients with cachexia and colorectal cancer.

However, Meier et al. confirmed that serum ferritin and transferrin levels have independent and excellent capabilities to determine prognosis in patients with end-stage liver disease [35]. A meta-analysis involving ten studies also showed that low pretreatment serum prealbumin level was significantly associated with poor prognosis in patients with liver cancer [18]. Considering the limited number of hepatobiliary and pancreatic cancer patients in our study, large-scale clinical research is required to further verify the prognostic value of prealbumin and transferrin in these populations. For lung cancer patients with cachexia, none of the three serum nutritional markers were statistically significant in predicting survival in our study.

We also assessed the association of serum hepatic proteins with short-term survival and QoL, which provides a good reference for comprehensively evaluating the prognostic value and clinical application prospects in cancer cachexia patients. Multivariate Cox regression analysis showed that the risk of mortality within 90 days were higher in patients with low albumin, prealbumin, and transferrin levels. Similarly, Miyamoto et al. found that the CRP/albumin ratio is an independent factor for predicting survival within two weeks [36]. Oyama et al. confirmed the value of the PNI in predicting life expectancy within 12 weeks in patients with end-stage gastric cancer [37]. We assessed QoL using the QLQ-C30 and found that patients with lower levels of serum hepatic proteins had a significantly poorer QoL. In Poisson generalized linear model, we found that low albumin, transferrin and prealbumin levels were all independent factor associated with impaired QoL. This is unsurprising as malnutrition and systemic inflammation are associated with a decline in QoL. Additionally, compared to albumin and transferrin, the discrimination value of prealbumin was significant in all domains of the QLQ-C30. This may be because the concentration of serum prealbumin reflects dietary intake rather than overall nutritional status [13].

This study had some limitations. First, owing to the limited number of patients with hepatobiliary and pancreatic cancer, the prognostic value in this subgroup may be biased. Second, this was an observational study, and there may be some unmeasured or measured confounders that could have affected the results. Third, all patients enrolled in our study were from a multicenter medical institution in China. Accordingly, the performance of serum nutritional markers in predicting survival in patients with cancer cachexia beyond the Chinese population is unknown. Large-scale international prospective clinical studies are required to overcome these biases.

In conclusion, serum hepatic protein levels are generally lower in cancer patients with cachexia. The present study reported that low albumin, prealbumin, and

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transferrin levels were associated with worse prognosis in patients with cancer cachexia. Albumin had the most accurate prognostic performance, followed by those of transferrin and prealbumin. The effect on survival was more significant in patients with advanced cancer. These results highlight the value of routinely assessing serum hepatic proteins in clinical practice, which may help predict the prognosis of patients with cancer cachexia.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-12056-5.

> **Supplementary Material 1.**

Availability of data and materials
All data generated or analysed during this study are included in this published article and this supplementary information files.

Declarations

Ethics approval and consent to participate
This study was in accordance with the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (reference number: 2013-82) and that of each participating hospital. All participants were informed of the purpose of the study and provided signed informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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