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# Triceps skinfold–albumin index significantly predicts the prognosis of cancer cachexia: A multicentre cohort study

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## Abstract

**Background** The fat mass and nutritional status play important roles in the onset and progression of cancer cachexia. The present study evaluated the joint prognostic value of the fat mass, as indicated by the triceps skinfold thickness (TSF), and the serum albumin level, for mortality in patients with cancer cachexia.

**Methods** We performed a multicentre cohort study including 5134 patients with cancer cachexia from January 2013 to April 2019. The sum of the TSF (mm) and serum albumin (g/L) was defined as the triceps skinfold–albumin index (TA). Harrell's *C* index, a time-dependent receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC) were used to evaluate the prognostic performance of the TA and other indices. Optimal stratification was used to identify the thresholds to define a low TA, and the association of the TA with all-cause mortality was evaluated using Kaplan–Meier analysis and Cox proportional hazard regression models.

**Results** The study enrolled 2408 women and 2726 men with a median age of 58.6 years and a median follow-up of 44 months. A total of 607 women (TA < 49.9) and 817 men (TA < 45.6) were classified as having a low TA. The TA showed better discrimination performance (*C* index = 0.621, 95% confidence interval [CI] = 0.607–0.636) to predict mortality in patients with cancer cachexia than the handgrip strength, the nutritional risk index, the prognostic nutritional index, the controlling nutritional status index, the systemic immune-inflammation index, the modified Glasgow prognostic score, and the TSF or albumin alone in the study population (all $P < 0.05$). The 1-, 3- and 5-year time-dependent ROC analyses (AUC = 0.647, 0.625 and 0.630, respectively) showed that the TA had the highest prognostic value among all indices investigated (all $P < 0.05$). Univariate analysis showed that a lower TA was associated with an increased death hazard (hazard ratio [HR] = 1.859, 95% CI = 1.677–2.062), regardless of the sex and cancer type. Multivariable survival analysis showed that a lower TA was independently associated with an increased death hazard (HR = 1.381, 95% CI = 1.223–1.560). This association was significantly strengthened in patients who did not receive curative chemotherapy (HR = 1.491, 95% CI = 1.298–1.713), those who had higher serum total protein levels (HR = 1.469, 95% CI = 1.284–1.681) and those with better physical performance (HR = 1.453, 95% CI = 1.271–1.662).

**Conclusions** This study defined and evaluated a new prognostic index, the TA, which may improve the selection of intervention strategies to optimize the survival of patients with cancer cachexia.

**Keywords** albumin; cancer cachexia; malnutrition; mortality; triceps skinfold

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## Introduction

Cancer cachexia is a multifactorial syndrome characterized by involuntary and ongoing skeletal muscle mass depletion with or without loss of fat mass.[1] The prevalence of cachexia is ~35% in cancer patients[2] and can reach 80–90% in patients with some cancer types, such as pancreatic and gastric cancers.[3] Conventional nutritional intervention is generally unable to reverse cancer cachexia and its associated progressive functional impairment.[1] Although multimodal approaches, including those aiming to improve the systemic inflammation, hypercatabolic status, appetite and physical activity of patients, have been introduced in recent years,[4] there is currently no treatment that has achieved a significant effect to tackle this refractory syndrome.[5] It was estimated that 20–25% of all cancer deaths can be ascribed to cachexia.[6] Therefore, elucidation of the prognostic indicators is essential to guide the development of novel management strategies for patients with cancer cachexia.

Malnutrition is a related pathological state that frequently develops in oncology populations and shares many core characteristics with cancer cachexia.[7] Thus, cancer malnutrition and cachexia have sometimes been used synonymously in the literature.[8] In the recently proposed Global Leadership Initiative on Malnutrition (GLIM) framework for diagnosing malnutrition, the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends the use of weight loss, a low body mass index (BMI) and sarcopenia to define the phenotypic dimension of malnutrition,[9] similar to the 2011 international consensus for diagnosing cancer cachexia.[1] In addition, serum biomarkers such as albumin have been included in other tools such as the nutritional risk index (NRI),[10] the prognostic nutritional index (PNI)[11] and the controlling nutritional status index (CONUT)[12] that are used to assess the nutritional status of patients and to indicate the onset and prognosis of cancer cachexia.[13]

Fat mass depletion is also a major feature of both cachexia and malnutrition in oncology populations.[1] A recent study found that cachexic gastric cancer patients with low subcutaneous adipose tissue (SAT) showed poorer survival than those with a high SAT,[14] suggesting that fat mass assessment may provide additional prognostic value in patients with cancer cachexia. In our previous work, we found that fat mass assessment using the triceps skinfold thickness (TSF) has better prognostic value than the BMI, mid-arm muscle circumference (MAMC), mid-arm circumference (MAC) and handgrip strength (HGS) to predict cancer survival.[15] In addition, we revealed that the TSF enhances the prognostic value of the GLIM criteria-defined malnutrition in patients with lung cancer.[16] Furthermore, by using the bioelectrical impedance analysis-derived fat mass index, we demonstrated that fat mass assessment outperforms HGS and GLIM-defined malnutrition in predicting cancer mortality.[17] These findings highlight the importance of including the fat mass as a component (in addition to the conventional assessments) for prognostic purposes in the context of both cachexia and malnutrition for oncology populations.

However, the potential joint prognostic value of the fat mass and a serum biomarker of cachexia/malnutrition in Asian populations with cancer cachexia remains largely unknown. In the present study conducted in a large, multicentre oncology cohort, we hypothesized that integrating the TSF as a reflection of the fat mass with the serum albumin level would provide significant prognostic information for patients with cancer cachexia. This information is useful to help develop novel intervention strategies to optimize the survival outcomes of cancer cachexia populations.

## Methods

### *Study design and population*

This was a hospital-based, multicentre cohort study. Patients were enrolled from a nationwide programme, the Investigation on Nutrition Status and its Clinical Outcome of Common Cancers (INSCOC) project, which was registered online at https://www.chictr.org.cn (identifier: ChiCTR1800020329). The detailed inclusion and exclusion criteria of the INSCOC project are shown in *Table S1*. In accordance with these criteria, we included 13 493 patients aged over 18 years who were diagnosed with cancer and/or were hospitalized for anticancer treatment from January 2013 to April 2019 at

multiple centres in four geographical regions (east, south, west and north) of China. We excluded 502 patients with non-solid malignancies and 217 patients with an unclear pathological diagnosis. This left 12 774 patients with 17 types of cancer for analysis. A flow chart of the patient inclusion is shown in *Figure S1*. The study was approved by the ethics committees of all participating institutions, and written consent forms were provided by all patients. All data were analysed anonymously, and the principles of the Declaration of Helsinki were followed.

## Data acquisition

Within the first 48 h after admission, the following baseline information was collected by a project-trained researcher via a comprehensive interview and physical examination: age, sex, smoking (active tobacco smoker), alcohol drinking (once a week or more frequent alcohol consumption in the past 1 year, regardless of amount), height, weight, BMI, MAC (non-dominant arm), TSF (non-dominant arm), HGS (non-dominant hand), calf circumference (CC, left calf), unintentional weight loss within and beyond 6 months, the Nutritional Risk Screening 2002 (NRS2002) score (≥3 indicating nutritional risk),[18] the Patient-Generated Subjective Global Assessment (PG-SGA) score,[19] the Karnofsky Performance Status (KPS) score[20] and the European Organization for Research and Treatment of Cancer QLQ-C30 (QLQ-C30) score.[21]

In the present study, the BMI was further categorized as underweight (<18.5 kg/m$^2$), normal (18.5 to <24 kg/m$^2$), overweight (24 to <28 kg/m$^2$) or obese (≥28 kg/m$^2$) based on the Chinese recommendations.[22] The detailed procedures and devices used to obtain the anthropometric information (height, weight, BMI, MAC, TSF, HGS, CC and weight loss) are shown in *Table S2*. The gastrointestinal symptoms of patients were extracted from the PG-SGA scale and analysed independently. For the QLQ-C30 score, the global quality of life (QOL) scale was used, with a higher score indicating a better overall QOL.[21]

The clinical information collected during hospitalization, including the cancer site, clinical stage, anticancer treatments used, serum indices, 30-day death, length of hospital stay, intensive care unit stay and cost were retrospectively retrieved from electronic medical records. All serum indices were measured at the clinical laboratories of the participating institutions using fasting blood samples drawn upon admission.

## Follow-up and main outcome

Annual follow-up was performed by a project-trained technician to obtain the survival information of each patient after enrolment via face-to-face or telephone interviews. The all-cause mortality was the main outcome of the present study, and the overall survival time was calculated as the time interval (months) between the first admission and the patient's date of death, the date of the last valid follow-up or April 2020.

## Definition of cancer cachexia

Based on the 2011 international consensus described by Fearon et al.,[1] cancer cachexia was retrospectively diagnosed if the patient met one or more of the following criteria: involuntary weight loss >5% over the past 6 months; BMI < 18.5 kg/m$^2$ (based on the Asian standards) and any degree of weight loss >2%; or muscle mass depletion (sarcopenia) and any degree of weight loss >2%. Sarcopenia was defined using the CC, based on a set of validated Asian thresholds (male <30 cm or female <29 cm).[23]

## Definition and grouping of the triceps skinfold–albumin index

The triceps skinfold–albumin index (TA) was defined as follows: TA = triceps skinfold thickness (mm) + albumin (g/L). We stratified the TA-related analyses by sex because the TSF differs by sex in terms of both the data distribution and prognostic value in patients with cancer.[15] We also categorized the continuous TA as a dichotomous variable to define the low (< cutoff) and normal (≥ cutoff) groups using the optimal stratification (OS)-defined thresholds for each gender. The OS method selects the threshold for a continuous factor by maximizing the between-group log-rank statistic for the overall survival and has been widely used in prognosis studies.[16]

## Statistical analysis

Continuous data are shown as the medians [25th percentile, 75th percentile] and were compared using a nonparametric Wilcoxon's rank-sum test. Categorical data were expressed as numbers (percentages) and compared using a $\chi^2$ test. Overall and group-specific distributions of the TA were visualized using a box plot. The two-variable correlation was assessed using Spearman's rank correlation analysis. Because prognostic indices, such as the geriatric nutrition risk index, can predict the prognosis of cancer cachexia,[10] we also calculated the baseline NRI, PNI, CONUT, systemic immune-inflammation index (SII) and modified Glasgow prognostic score (mGPS) to compare their prognostic value with the TA according to the following approaches: NRI = (1.519 × serum albumin, g/L) + (41.7 × present

weight/usual weight); PNI = 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count ($mm^3$); SII = peripheral platelet × neutrophil/lymphocyte counts[24]; and CONUT includes the serum albumin level, total lymphocyte counts and serum total cholesterol level. The detailed scoring method used by the CONUT has been described previously[24]; mGPS includes the serum C-reactive protein level and albumin level. The detailed scoring method used by the mGPS has been described previously.[24] Harrell's *C* index,[25] integrated discrimination improvement (IDI),[26] continuous net reclassification improvement (cNRI)[27] and time-dependent receiver operating characteristic (ROC) curve estimation were calculated to evaluate and compare the discrimination performance of the prognostic indices. The calculation of *C* index implemented 1000 iterations of bootstrap resampling (R package 'boot'), and the IDI and cNRI were adjusted with 1000 iterations of perturbation resampling (R package 'survIDINRI') to obtain unbiased estimates. The time-dependent *C* index was calculated and visualized every month within a 5-year interval, following a 1000-sample bootstrap cross-validation and 10 iterations of 10-fold cross-validation to improve robustness, respectively.

A restricted cubic spline (RCS) was used to flexibly analyse the potential nonlinear associations of the continuous TA with sex-specific survival. The associations between the TA categories and survival were evaluated using Kaplan–Meier curves and log-rank tests. The univariate Kaplan–Meier analysis was also stratified in different sex and cancer-type subgroups. Multivariable-adjusted Cox proportional hazards models were used, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to estimate the association between the TA and mortality. Kaplan–Meier curves and the Schoenfeld individual test were used to visually and statistically estimate the proportional hazards assumption for each covariate adjusted.

Incremental models with increasing numbers of covariates were created. A dual-direction stepwise method based on the Bayesian information criterion (BIC) was used to help select the significant covariates. Model 0 was an unadjusted crude model. Model 1 was adjusted for the age at baseline and sex. Model 2 was adjusted for age, sex and the BIC-screened independent predictors, including the tumour stage, radical surgery, curative chemotherapy, HGS, total protein level, the PG-SGA score and cancer type. Model 3 was adjusted for all variables in Model 2, plus the prealbumin level, CC, NRS2002 score, KPS score and the global QOL score.

Because the majority of patients in the study population had advanced or metastatic cancer ($n$ = 3450, 67.2%), sensitivity analyses were performed to test the robustness of the multivariate Cox regression models by excluding the patients who died within the first 3 months ($n$ of deaths = 275, 18%) after enrolment to maximize statistical power (Model 4). Subgroup analyses were performed in different strata of the adjusting variables to evaluate whether there was modification of the associations observed in the overall population and to determine whether the TA was applicable across different subgroups. We carried out subgroup analyses based on the patient age (<60 vs. ≥60 years), sex (female vs. male), clinical stage (I to II vs. III to IV), radical surgery (yes vs. no), curative chemotherapy (yes vs. no), HGS (normal vs. low, low HGS was defined as <18 kg for women or <28 kg for men), CC (normal vs. low), total protein (<60 vs. ≥60 g/L), prealbumin (<200 vs. ≥200 mg/L), NRS2002 score (<3 vs. ≥3), PG-SGA score (<4 vs. ≥4), KPS score (<80 vs. ≥80), global QOL score (<80 vs. ≥80) and cancer type (lung cancer, colorectal cancer, gastric cancer, other gastrointestinal cancers [including biliary, oesophageal, gastric stromal, liver and pancreatic cancers], breast cancer and other cancers [including lymphoma and bladder, brain, cervical, endometrial, nasopharyngeal and ovarian cancers]). Multiplicative interactions were tested by adjusting the cross-product terms of the TA and other covariates. Those covariates showing a statistically significant multiplicative interaction ($P < 0.05$) were defined as potential effect modifiers. All tests were two-sided, and $P < 0.05$ was regarded as statistically significant unless otherwise specified. All analyses were performed using R (Version 3.6.3, http://www.rproject.org).

# Results

## Cohort overview

Among the 12 774 patients investigated, cancer cachexia was diagnosed in 5134 (40%) patients, 2408 of whom were women and 2726 were men. The patients had a median age of 58.6 years. The detailed baseline characteristics of the cachexia cohort are shown in the overall column of *Table 1*. The tumours were most frequently located in the lung (21.1%), colorectum (21.0%), stomach (16.0%), breast (10.7%), oesophagus (8.8%) and nasopharynx (5.1%). The predominant clinical stages were III (38.5%) and IV (28.7%). There were 1909 (37.2%) underweight patients, 2535 (49.4%) patients with a normal weight, 565 (11.0%) overweight patients and 125 (2.4%) obese patients. There were 1514 deaths among 5134 patients during a median follow-up of 44 months.

## Distribution of triceps skinfold–albumin index

The distribution of the TA, as stratified by different clinical characteristics, is shown in *Figure 1*. In general, women had higher TA values than men. A cancer-specific analysis showed that patients with breast, cervical and ovarian cancers had relatively higher TA values, whereas lower TA values were

**Table 1** Baseline characteristics of the study population

| Characteristics | Overall ($n$ = 5134), range [11.2–422.0][a] | Triceps skinfold–albumin index | | $P$ |
|---|---|---|---|---|
| | | Normal ($n$ = 3710), range [45.6–422.0][b] | Low ($n$ = 1424), range [11.2–49.8][c] | |
| Age (years) | 58.6 [49.8, 65.4][d] | 57.3 [48.7, 64.5] | 61.3 [53.6, 67.9] | <0.001 |
| Sex (male) | 2726 (53.1)[e] | 1909 (51.5) | 817 (57.4) | <0.001 |
| Body mass index (kg/m$^2$) | 21.3 [18.8, 24.0] | 22.3 [20.2, 24.8] | 19.5 [17.7, 22.3] | <0.001 |
| Body mass index category | | | | <0.001 |
| Underweight (<18.5) | 1909 (37.2) | 1095 (29.5) | 814 (57.2) | |
| Normal (18.5 to <24) | 2535 (49.4) | 2006 (54.1) | 529 (37.1) | |
| Overweight (24 to <28) | 565 (11.0) | 493 (13.3) | 72 (5.1) | |
| Obese (≥28) | 125 (2.4) | 116 (3.1) | 9 (0.6) | |
| Smoking (yes) | 2224 (43.3) | 1533 (41.3) | 691 (48.5) | <0.001 |
| Alcohol drinking (yes) | 1044 (20.3) | 739 (19.9) | 305 (21.4) | 0.248 |
| Cancer site | | | | <0.001 |
| Lung | 1083 (21.1) | 774 (20.9) | 309 (21.7) | |
| Colorectum | 1078 (21.0) | 803 (21.6) | 275 (19.3) | |
| Stomach | 821 (16.0) | 497 (13.4) | 324 (22.8) | |
| Breast | 550 (10.7) | 496 (13.4) | 54 (3.8) | |
| Oesophagus | 450 (8.8) | 279 (7.5) | 171 (12.0) | |
| Nasopharynx | 261 (5.1) | 229 (6.2) | 32 (2.2) | |
| Liver | 177 (3.4) | 111 (3.0) | 66 (4.6) | |
| Cervix | 177 (3.4) | 146 (3.9) | 31 (2.2) | |
| Lymphoma | 126 (2.5) | 87 (2.3) | 39 (2.7) | |
| Ovary | 144 (2.8) | 113 (3.0) | 31 (2.2) | |
| Pancreas | 115 (2.2) | 71 (1.9) | 44 (3.1) | |
| Biliary | 48 (0.9) | 21 (0.6) | 27 (1.9) | |
| Endometrium | 40 (0.8) | 31 (0.8) | 9 (0.6) | |
| Bladder | 30 (0.6) | 23 (0.6) | 7 (0.5) | |
| Prostate | 17 (0.3) | 14 (0.4) | 3 (0.2) | |
| Brain | 8 (0.2) | 8 (0.2) | 0 (0.0) | |
| Gastric stroma | 9 (0.2) | 7 (0.2) | 2 (0.1) | |
| Clinical stage | | | | <0.001 |
| I | 575 (11.2) | 456 (12.3) | 119 (8.4) | |
| II | 1109 (21.6) | 851 (22.9) | 258 (18.1) | |
| III | 1979 (38.5) | 1455 (39.2) | 524 (36.8) | |
| IV | 1471 (28.7) | 948 (25.6) | 523 (36.7) | |
| Anticancer therapies | | | | |
| Radical surgery | 2132 (41.5) | 1551 (41.8) | 581 (40.8) | 0.533 |
| Curative chemotherapy | 823 (16.0) | 573 (15.4) | 250 (17.6) | 0.071 |
| Adjuvant chemotherapy | 965 (18.8) | 753 (20.3) | 212 (14.9) | <0.001 |
| Chemotherapy for metastasis | 471 (9.2) | 341 (9.2) | 130 (9.1) | 0.988 |
| Curative radiotherapy | 255 (5.0) | 160 (4.3) | 95 (6.7) | 0.001 |
| Total protein (g/L) | 66.8 [61.5, 71.4] | 68.5 [64.0, 72.6] | 61.5 [56.7, 66.5] | <0.001 |
| Prealbumin (mg/L) | 200.0 [149.5, 240.0] | 210.0 [170.0, 255.0] | 150.0 [105.0, 204.1] | <0.001 |
| Albumin (g/L) | 38.0 [34.1, 41.6] | 39.8 [36.7, 42.7] | 32.9 [29.6, 35.6] | <0.001 |
| Transferrin (g/L) | 2.2 [1.9, 2.6] | 2.3 [1.9, 2.7] | 2.1 [1.7, 2.5] | <0.001 |
| Haemoglobin (g/L) | 121.0 [106.0, 134.0] | 125.0 [112.0, 137.0] | 109.5 [95.0, 123.0] | <0.001 |
| White blood cells (× 10$^9$/L) | 6.3 [4.8, 8.4] | 6.1 [4.8, 8.0] | 6.9 [5.1, 9.6] | <0.001 |
| Platelets (× 10$^9$/L) | 230.0 [178.0, 293.0] | 228.0 [180.0, 288.0] | 238.0 [174.8, 317.0] | 0.003 |
| Neutrophils (× 10$^9$/L) | 4.0 [2.8, 5.9] | 3.8 [2.7, 5.4] | 4.8 [3.1, 7.3] | <0.001 |
| Lymphocytes (× 10$^9$/L) | 1.4 [1.0, 1.9] | 1.5 [1.1, 2.0] | 1.2 [0.9, 1.7] | <0.001 |
| Neutrophil-to-lymphocyte ratio | 2.8 [1.8, 4.8] | 2.5 [1.7, 4.0] | 3.9 [2.2, 7.2] | <0.001 |
| C-reactive protein (mg/L) | 4.5 [2.6, 24.0] | 3.3 [1.8, 14.4] | 15.4 [3.4, 53.0] | <0.001 |
| Mid-arm circumference (cm) | 25.0 [23.0, 27.5] | 26.0 [24.0, 28.0] | 23.5 [21.5, 25.2] | <0.001 |
| Triceps skinfold thickness (mm) | 15.0 [10.0, 20.0] | 18.0 [13.0, 22.0] | 9.0 [6.0, 12.0] | <0.001 |
| Handgrip strength (kg) | 22.3 [16.1, 29.7] | 23.2 [17.2, 30.5] | 19.8 [13.8, 26.7] | <0.001 |
| Calf circumference (cm) | 32.0 [30.0, 34.0] | 32.5 [30.5, 35.0] | 30.0 [28.0, 32.0] | <0.001 |
| Weight loss within 6 months (%) | 0.0 [0.0, 3.5] | 0.0 [0.0, 0.0] | 4.2 [0.0, 7.5] | <0.001 |
| NRS2002 score (continuous) | 4.0 [2.0, 4.0] | 4.0 [2.0, 4.0] | 4.0 [4.0, 4.0] | <0.001 |
| NRS2002 score (≥3) | 3805 (74.1) | 2520 (67.9) | 1285 (90.2) | <0.001 |
| PG-SGA score (continuous) | 7.0 [4.0, 11.0] | 6.0 [3.0, 10.0] | 10.0 [6.0, 13.0] | <0.001 |
| PG-SGA category | | | | <0.001 |
| 0–1 | 516 (10.1) | 470 (12.7) | 46 (3.2) | |
| 2–3 | 674 (13.1) | 571 (15.4) | 103 (7.2) | |
| 4–8 | 1884 (36.7) | 1440 (38.8) | 444 (31.2) | |

(*Continues*)


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**Table 1** (continued)

| Characteristics | Overall ($n$ = 5134), range [11.2–422.0][a] | Triceps skinfold–albumin index | | $P$ |
|---|---|---|---|---|
| | | Normal ($n$ = 3710), range [45.6–422.0][b] | Low ($n$ = 1424), range [11.2–49.8][c] | |
| ≥9 | 2060 (40.1) | 1229 (33.1) | 831 (58.4) | |
| Gastrointestinal symptoms (overall) | 2731 (53.2) | 1798 (48.5) | 933 (65.5) | <0.001 |
| Anorexia | 1009 (19.7) | 615 (16.6) | 394 (27.7) | <0.001 |
| Nausea | 469 (9.1) | 300 (8.1) | 169 (11.9) | <0.001 |
| Vomiting | 337 (6.6) | 195 (5.3) | 142 (10.0) | <0.001 |
| Mouth sores | 56 (1.1) | 44 (1.2) | 12 (0.8) | 0.363 |
| Constipation | 403 (7.8) | 258 (7.0) | 145 (10.2) | <0.001 |
| Diarrhoea | 233 (4.5) | 163 (4.4) | 70 (4.9) | 0.465 |
| Dry mouth | 375 (7.3) | 245 (6.6) | 130 (9.1) | 0.002 |
| Things taste funny or have no taste | 293 (5.7) | 192 (5.2) | 101 (7.1) | 0.010 |
| Smells bother me | 138 (2.7) | 90 (2.4) | 48 (3.4) | 0.075 |
| Dysphagia | 353 (6.9) | 209 (5.6) | 144 (10.1) | <0.001 |
| Feel full quickly | 462 (9.0) | 291 (7.8) | 171 (12.0) | <0.001 |
| Abdominal pain | 519 (10.1) | 351 (9.5) | 168 (11.8) | 0.015 |
| Other | 122 (2.4) | 82 (2.2) | 40 (2.8) | 0.247 |
| KPS score | 90.0 [80.0, 90.0] | 90.0 [80.0, 90.0] | 80.0 [70.0, 90.0] | <0.001 |
| Global QOL score | 66.7 [50.0, 75.0] | 66.7 [50.0, 83.3] | 50.0 [41.7, 66.7] | <0.001 |
| Prognostic scores | | | | |
| NRI | 94.9 [88.5, 100.9] | 97.9 [93.0, 102.7] | 86.2 [81.1, 91.1] | <0.001 |
| PNI | 45.4 [40.5, 50.0] | 47.5 [43.6, 51.4] | 39.2 [35.0, 43.0] | <0.001 |
| CONUT | 2.0 [1.0, 4.0] | 2.0 [1.0, 3.0] | 4.0 [3.0, 6.0] | <0.001 |
| SII | 645.8 [365.9, 195.2] | 587.8 [340.3, 89.9] | 929.7 [482.3, 818.4] | <0.001 |
| mGPS | 0.0 [0.0, 1.0] | 0.0 [0.0, 1.0] | 1.0 [0.0, 2.0] | <0.001 |
| Short-term outcomes | | | | |
| 30-day mortality | 98 (1.9) | 47 (1.3) | 51 (3.6) | <0.001 |
| Length of hospital stay (days) | 13.0 [8.0, 19.0] | 12.0 [7.0, 19.0] | 13.0 [8.0, 20.0] | <0.001 |
| Intensive care unit stay (yes) | 1008 (19.6) | 703 (18.9) | 305 (21.4) | 0.051 |
| Cost (10 000 CNY) | 2.3 [1.2, 5.3] | 2.1 [1.1, 5.0] | 2.9 [1.4, 5.8] | <0.001 |

Abbreviations: CNY, Chinese Yuan; CONUT, controlling nutritional status index; KPS, Karnofsky Performance Status; mGPS, modified Glasgow prognostic score; NRI, nutritional risk index; NRS2002, Nutritional Risk Screening 2002; PG-SGA, Patient-Generated Subjective Global Assessment; PNI, prognostic nutritional index; QOL, quality of life; SII, systemic immune-inflammation index; TA, triceps skinfold–albumin index.

[a]Range of TA, female [11.2–360.0] and male [13.4–422.0].
[b]Range of TA, female [49.9–360.0] and male [45.6–422.0].
[c]Range of TA, female [11.2–49.8] and male [13.4–45.5].
[d]Median [25th percentile, 75th percentile], all such values.
[e]Number (percentage), all such values.

predominantly observed in individuals with gastrointestinal cancer types, such as oesophageal, gastric, liver and pancreatic cancers. In addition, the TA value was relatively lower in patients with an older age, lower BMI, advanced tumour, nutritional risk, malnutrition and systemic inflammation (as indicated by the neutrophil-to-lymphocyte ratio).

## *Correlation of the triceps skinfold–albumin index with clinical findings*

Sex-specific Spearman's rank correlation tests were performed to assess the degree of relevance for the associations of the continuous TA with various clinical features (*Figure S2*). Similar results were observed for both genders, showing a positive correlation between the TA and BMI, CC, HGS, total protein, prealbumin, haemoglobin, KPS score, global QOL score, NRI and PNI, and a negative correlation between the TA and the neutrophil-to-lymphocyte ratio, C-reactive protein level, NRS2002 score, PG-SGA score, CONUT, SII and mGPS (all $P < 0.05$).

## *Prognostic value of the triceps skinfold–albumin index*

Harrell's *C* index of the TA was statistically compared to those calculated for the TSF, albumin, HGS, NRI, PNI, CONUT, SII and mGPS in the overall population and in each sex. The results showed that the TA had the highest prognostic value in the overall population, with a *C* index = 0.621 (95% CI = 0.607–0.636) compared to the TSF (0.607, 95% CI = 0.591–0.622), albumin (0.590, 95% CI = 0.574–0.605), HGS (0.514, 95% CI = 0.499–0.530), NRI (0.588, 95% CI = 0.573–0.603), PNI (0.589, 95% CI = 0.574–0.604), CONUT (0.582, 95% CI = 0.574–0.604), SII (0.560, 95% CI = 0.544–

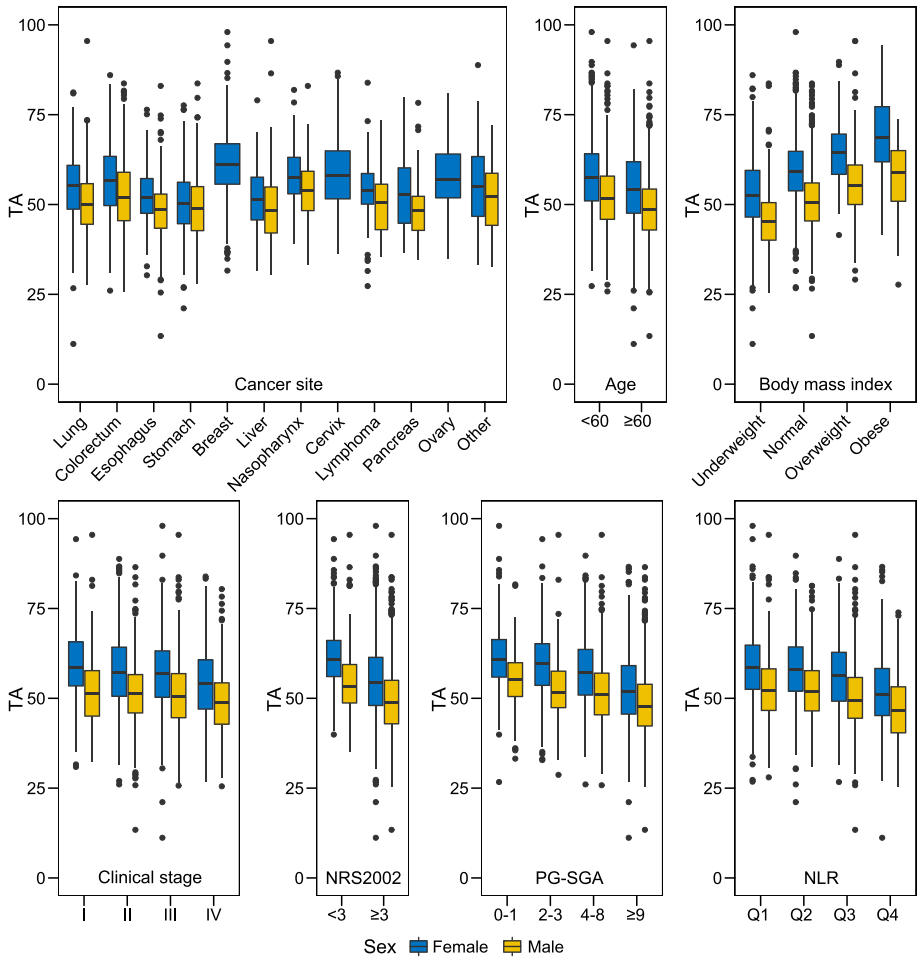


**Figure 1** Distribution of the triceps skinfold–albumin index (TA) stratified by patient characteristics. NLR, neutrophil-to-lymphocyte ratio; NRS2002, Nutritional Risk Screening 2002 score; PG-SGA, Patient-Generated Subjective Global Assessment score; Q, quartile

0.575) and mGPS (0.596, 95% CI = 0.573–0.619) (all $P < 0.001$). In the sex-specific analysis, the TA showed higher prognostic value than the TSF, HGS, CONUT, SII and mGPS, while being comparable to the albumin level, NRI and PNI in women. In contrast, the TA showed higher prognostic value than the albumin level, HGS, NRI, PNI, CONUT, SII and mGPS, whereas it was comparable to the TSF in men. Harrell's *C* index of the TA was further compared to those calculated for other indices in different age (<60 vs. ≥60) and tumour stage (I–II, III and IV) subgroups (*Table S3*). The TA showed higher prognostic value than other indices in both younger and older patients (all $P < 0.05$) and was comparable to the TSF in older patients ($P = 0.778$). In the tumour stage-specific analysis, the TA was comparable to the TSF in patients with Stage I–II disease ($P = 0.070$) and to the PNI ($P = 0.068$) in patients with Stage III disease. It was also comparable to the TSF ($P = 0.586$) and SII ($P = 0.061$) in patients with Stage IV disease. In contrast, the TA showed higher prognostic value than other indices in the tumour stage-specific analysis (all $P < 0.05$).

The IDI results showed that the TA had significant discrimination improvement compared to the other indices in the overall population. In the sex-specific analysis, the TA showed higher discrimination performance than the TSF, albumin, HGS, NRI, SII and mGPS, while being comparable to the PNI and CONUT in women. In contrast, the TA showed higher discrimination performance than all other indices except being comparable to the TSF in men. Additionally, the cNRI results showed that the TA had significant discrimination improvement than all other indices except being comparable to the TSF in the overall population and in men (*Table 2*).

The 1-, 3- and 5-year time-dependent ROC curves and the corresponding area under the curve (AUC) of the TA were visually and statistically compared to those calculated for the TSF, albumin, HGS, NRI, PNI, CONUT, SII and mGPS in the overall population and in each sex (*Figure S3*). The TA had the highest time-dependent AUC compared to all other indices in the overall population at all three time points. In women, the TA had higher time-dependent AUC than the TSF, HGS, SII and mGPS, while being comparable to

**Table 2** Discrimination performance of the TA compared to the TSF, albumin, HGS, NRI, PNI, CONUT, SII and mGPS

| Index | Harrell's *C* index (95% CI)[a] | | |
|---|---|---|---|
| | Overall ($n$ = 5134) | Female ($n$ = 2408) | Male ($n$ = 2726) |
| TA | 0.621 (0.607–0.636) | 0.628 (0.605–0.652) | 0.590 (0.571–0.609) |
| TSF | 0.607 (0.591–0.622) | 0.593 (0.567–0.618) | 0.587 (0.567–0.607) |
| Albumin | 0.590 (0.574–0.605) | 0.620 (0.595–0.645) | 0.554 (0.535–0.574) |
| HGS | 0.514 (0.499–0.530) | 0.575 (0.551–0.599) | 0.560 (0.541–0.579) |
| NRI | 0.588 (0.573–0.603) | 0.614 (0.590–0.639) | 0.559 (0.539–0.578) |
| PNI | 0.589 (0.574–0.604) | 0.624 (0.600–0.649) | 0.556 (0.536–0.575) |
| CONUT | 0.582 (0.565–0.600) | 0.615 (0.587–0.644) | 0.552 (0.530–0.574) |
| SII | 0.560 (0.544–0.575) | 0.587 (0.561–0.613) | 0.466 (0.447–0.485) |
| mGPS | 0.596 (0.573–0.619) | 0.636 (0.599–0.673) | 0.555 (0.526–0.584) |
| Pairwise *P* | | | |
| TA vs. TSF | <0.001 | <0.001 | 0.281 |
| TA vs. albumin | <0.001 | 0.415 | <0.001 |
| TA vs. HGS | <0.001 | <0.001 | 0.007 |
| TA vs. NRI | <0.001 | 0.197 | <0.001 |
| TA vs. PNI | <0.001 | 0.753 | <0.001 |
| TA vs. CONUT | <0.001 | 0.039 | <0.001 |
| TA vs. SII | <0.001 | 0.013 | <0.001 |
| TA vs. mGPS | <0.001 | <0.001 | <0.001 |

Abbreviations: CI, confidence interval; cNRI, continuous net reclassification improvement; CONUT, controlling nutritional status index; HGS, handgrip strength; IDI, integrated discrimination improvement; mGPS, modified Glasgow prognostic score; NRI, nutritional risk index; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; TA, triceps skinfold–albumin index; TSF, triceps skinfold thickness.
[a]Adjusted with 1000 iterations of bootstrap resampling.
[1b]Adjusted with 1000 iterations of perturbation resampling.

**Table 2** (continued)

| Index | IDI (95% CI)[b], TA vs. other index | | | cNRI (95% CI)[b], TA vs. other index | | |
|---|---|---|---|---|---|---|
| | Overall ($n$ = 5134) | Female ($n$ = 2408) | Male ($n$ = 2726) | Overall ($n$ = 5134) | Female ($n$ = 2408) | Male ($n$ = 2726) |
| TA | — | — | — | — | — | — |
| TSF | 0.005 (0.000–0.009) | 0.012 (0.005–0.018) | 0.000 (−0.007 to 0.005) | 0.032 (−0.022 to 0.109) | 0.192 (0.041–0.255) | −0.018 (−0.103 to 0.064) |
| Albumin | 0.018 (0.014–0.022) | 0.010 (0.001–0.018) | 0.014 (0.008–0.021) | 0.191 (0.145–0.218) | 0.133 (0.045–0.213) | 0.171 (0.106–0.212) |
| HGS | 0.028 (0.022–0.037) | 0.021 (0.010–0.035) | 0.009 (0.000–0.019) | 0.215 (0.169–0.252) | 0.168 (0.075–0.251) | 0.070 (0.002–0.130) |
| NRI | 0.018 (0.012–0.022) | 0.012 (0.005–0.019) | 0.013 (0.007–0.020) | 0.194 (0.141–0.228) | 0.160 (0.065–0.216) | 0.180 (0.098–0.213) |
| PNI | 0.027 (0.019–0.037) | 0.009 (−0.001 to 0.020) | 0.018 (0.009–0.027) | 0.221 (0.163–0.252) | 0.102 (0.012–0.181) | 0.137 (0.095–0.188) |
| CONUT | 0.017 (0.008–0.023) | 0.007 (−0.002 to 0.016) | 0.013 (0.004–0.021) | 0.153 (0.093–0.194) | 0.108 (0.015–0.184) | 0.140 (0.056–0.193) |
| SII | 0.029 (0.020–0.037) | 0.025 (0.015–0.041) | 0.018 (0.010–0.028) | 0.228 (0.183–0.262) | 0.226 (0.144–0.285) | 0.137 (0.101–0.181) |
| mGPS | 0.020 (0.011–0.028) | 0.011 (0.001–0.023) | 0.015 (0.006–0.023) | 0.156 (0.105–0.202) | 0.108 (0.025–0.181) | 0.144 (0.047–0.177) |
| Pairwise *P* | | | | | | |
| TA vs. TSF | 0.039 | <0.001 | 0.891 | 0.275 | <0.001 | 0.634 |
| TA vs. albumin | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| TA vs. HGS | <0.001 | <0.001 | 0.040 | <0.001 | <0.001 | 0.040 |
| TA vs. NRI | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| TA vs. PNI | <0.001 | 0.119 | <0.001 | <0.001 | 0.040 | <0.001 |

**Table 2** (continued)

| Index | IDI (95% CI)[b], TA vs. other index | | | cNRI (95% CI)[b], TA vs. other index | | |
|---|---|---|---|---|---|---|
| | Overall ($n$ = 5134) | Female ($n$ = 2408) | Male ($n$ = 2726) | Overall ($n$ = 5134) | Female ($n$ = 2408) | Male ($n$ = 2726) |
| TA vs. CONUT | <0.001 | 0.196 | <0.001 | <0.001 | <0.001 | <0.001 |
| TA vs. SII | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| TA vs. mGPS | <0.001 | 0.040 | <0.001 | <0.001 | <0.001 | 0.020 |

Abbreviations: CI, confidence interval; cNRI, continuous net reclassification improvement; CONUT, controlling nutritional status index; HGS, handgrip strength; IDI, integrated discrimination improvement; mGPS, modified Glasgow prognostic score; NRI, nutritional risk index; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; TA, triceps skinfold–albumin index; TSF, triceps skinfold thickness.
[a]Adjusted with 1000 iterations of bootstrap resampling.
[b]Adjusted with 1000 iterations of perturbation resampling.

the albumin and PNI at all three time points. The TA also showed higher time-dependent AUC than the NRI and CONUT at the 1- and 5-year time points, respectively, while being comparable to the NRI and CONUT at other time points. In men, the TA had higher time-dependent AUC compared to all other indices while being comparable to the TSF at all three time points. The TA had the highest time-dependent AUC compared to all other indices in the overall population at all three time points. The time-dependent *C* index for all indices was assessed monthly, and the values are shown in *Figure 2*. The TA had the highest time-dependent *C* index compared to all other indices in the overall population and in men within the entire 5-year interval (*Figure 2A,B,E,F*). In women, the TA had higher time-dependent *C* index than all other indices in the 5-year interval, but was comparable to the TSF during the 3- to 5-year interval (*Figure 2C,D*).

## *Optimal threshold and restricted cubic spline analysis*

Based on the OS method, the optimal thresholds for the TA were determined to be 49.9 for women and 45.6 for men (*Figure 3A,B*). Based on these thresholds, 607 women (TA $<$ 49.9) and 817 men (TA $<$ 45.6) were classified into the low TA group. After setting the calculated thresholds as the reference value (HR = 1), an RCS analysis showed that the continuous TA was associated with reduced mortality in both gender strata (both $P < 0.001$, *Figure 3C,D*).

## *Relationship between the triceps skinfold–albumin index category and clinical characteristics*

The clinical characteristics of patients stratified by the OS-defined TA categories are presented in *Table 1*. Compared to the group with a normal TA, the low TA group was associated with a higher value/rate of age, male sex, smoking, curative radiotherapy, white blood cells, platelets, neutrophils, neutrophil-to-lymphocyte ratio, C-reactive protein, weight loss, NRS2002 score, PG-SGA score, gastrointestinal symptoms (overall, anorexia, nausea, vomiting, constipation, dry mouth, things taste funny or have no taste, dysphagia, feel full quickly and abdominal pain), CONUT, SII and mGPS and was associated with a lower value/rate for the BMI, adjuvant therapy, total protein, prealbumin, albumin, transferrin, haemoglobin, lymphocytes, MAC, TSF, HGS, CC, KPS score, global QOL score, NRI and PNI. As was expected, the cancer types and clinical stage were also different between the low and normal TA groups. Additionally, a univariate analysis of the short-term outcomes showed that a lower TA was associated with a higher rate of 30-day mortality, longer length of hospital stay and higher costs during hospitalization (all $P < 0.05$).

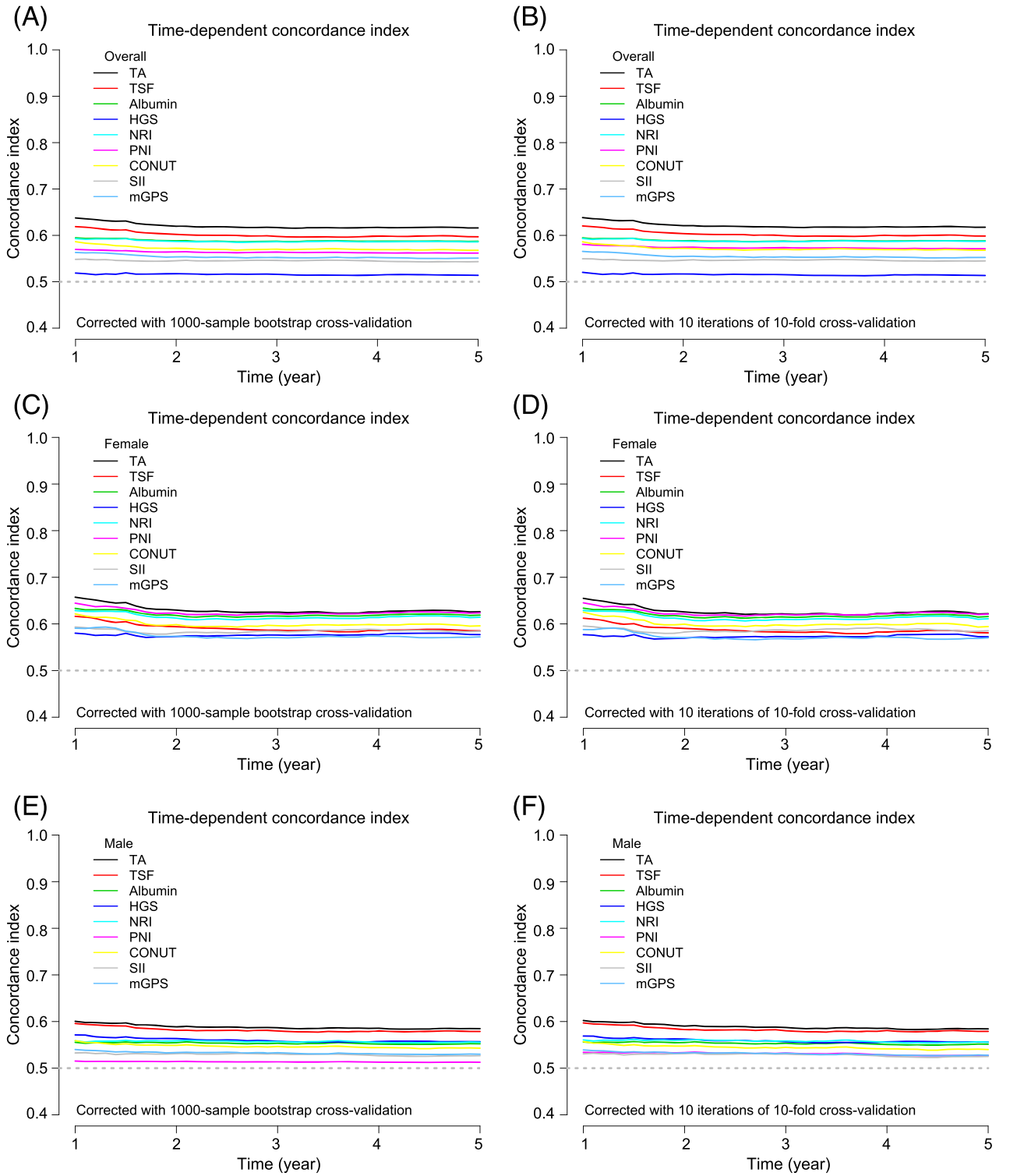


**Figure 2** Time-dependent C index. (A) Bootstrap cross-validated time-dependent C index in the overall population. (B) Ten-fold cross-validated time-dependent C index in the overall population. (C) Bootstrap cross-validated time-dependent C index in women. (D) Ten-fold cross-validated time-dependent C index in women. (E) Bootstrap cross-validated time-dependent C index in men. (F) Ten-fold cross-validated time-dependent C index in men. CONUT, controlling nutritional status index; HGS, handgrip strength; mGPS, modified Glasgow prognostic score; NRI, nutritional risk index; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; TA, triceps skinfold–albumin index; TSF, triceps skinfold thickness

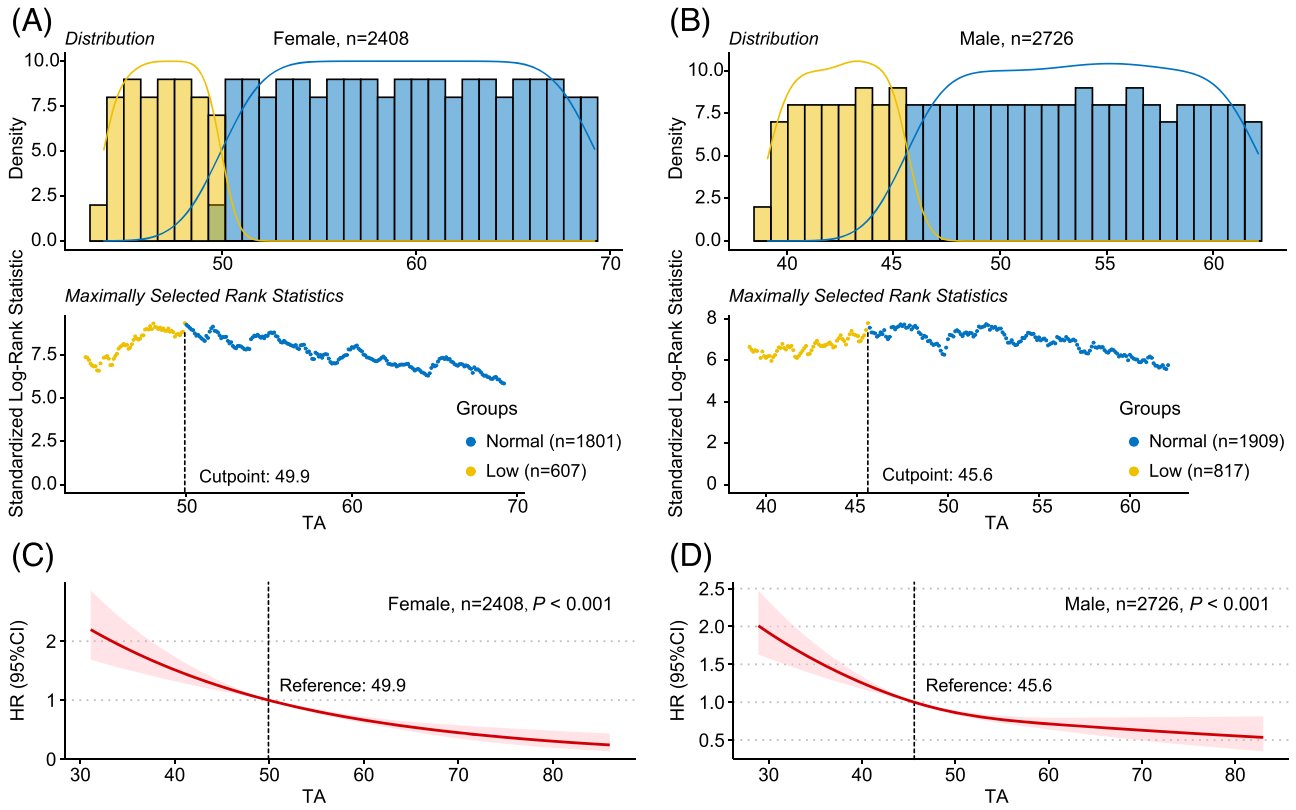


**Figure 3** Optimal stratification for cutoff identification and restricted cubic spine (RCS) analysis. (A) Selection of the optimal triceps skinfold–albumin index (TA) cutoff in women. (B) Selection of the optimal TA cutoff in men. (C) RCS analysis of the association between the TA and survival in women. (D) RCS analysis of the association between the TA and survival in men. CI, confidence interval; HR, hazard ratio

## *Kaplan–Meier analysis*

Kaplan–Meier curves demonstrated that patients with a lower TA had a poorer overall survival than those in the normal group in the overall population ($P < 0.001$). We also replicated this analysis in different patient subgroups. The results showed that the association observed in the overall population was sustained in all strata investigated, including women, men and those with lung cancer, colorectal cancer, gastric cancer, other gastrointestinal cancers, breast cancer and other cancers (*Figures 4* and *S4*, all $P < 0.05$).

## *Multivariable survival analysis*

The results of the multivariable Cox proportional hazards model analyses of the associations between the TA and mortality are shown in *Table 3*. The TA was analysed as a continuous variable, per each standard deviation and as a categorical variable. In the fully adjusted model (Model 3), the decreasing TA was independently associated with an increased death hazard in the overall population (HR = 1.017, 95% CI = 1.011–1.025), in women (HR = 1.019, 95% CI = 1.008–1.030) and in men (HR = 1.016, 95% CI = 1.007–1.025). Similarly, when the TA was analysed following separation by one standard deviation, consistent results were observed in the overall population (HR = 1.292, 95% CI = 1.171–1.427), women (HR = 1.259, 95% CI = 1.105–1.435) and men (HR = 1.292, 95% CI = 1.125–1.486). In addition, after dichotomizing the TA based on the sex-specific OS thresholds, patients in the low TA group had an increased death hazard compared those in the normal TA group (HR = 1.381, 95% CI = 1.223–1.560). A sensitivity analysis showed that these associations were all sustained after excluding those patients died within the first 3 months after enrolment (Model 4).

## *Interaction and subgroup analysis*

The fully adjusted models were repeated in different covariate subgroups to study the effect modifications, and all covariates were statistically screened for potential interactive effects (*Figure 5*). The use of curative chemotherapy, total protein and KPS score were identified as potential effect modifiers (all $P < 0.05$). The positive association between the low TA and mortality observed in the overall population (HR = 1.381, 95% CI = 1.223–1.560) was strengthened in pa-

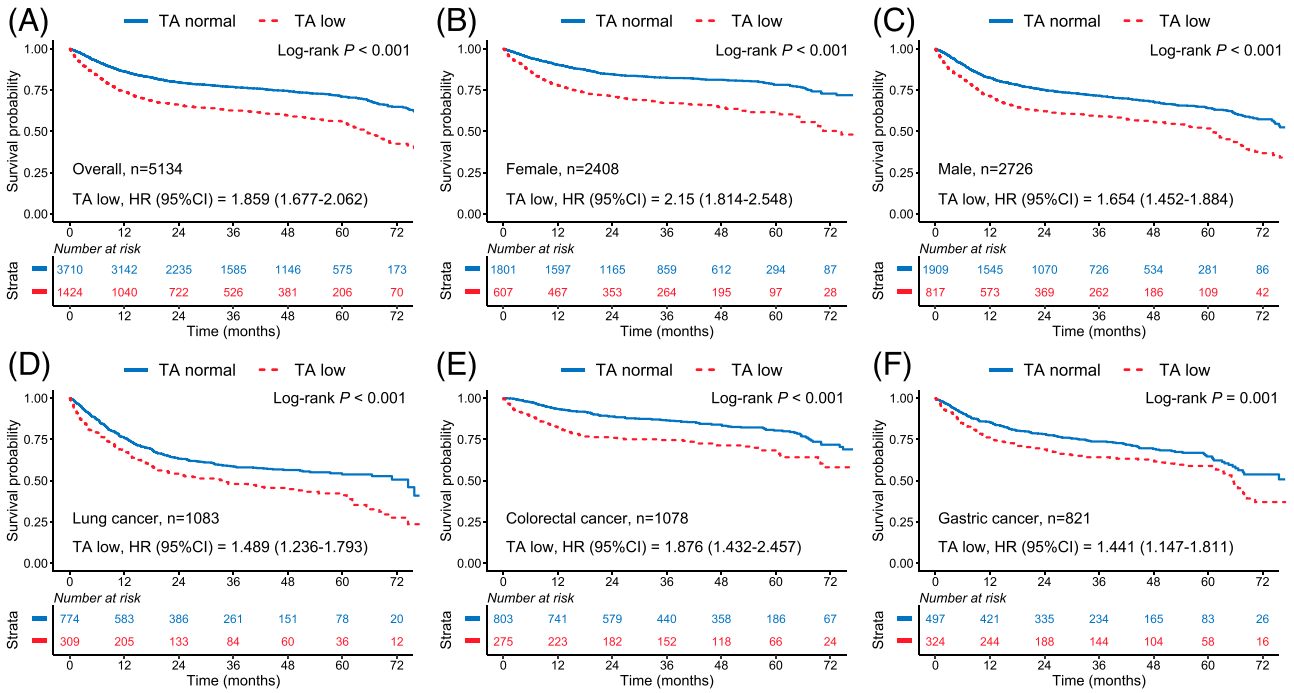


**Figure 4** Analysis of the associations of the triceps skinfold–albumin index (TA) with survival. (A) Kaplan–Meier curves in the overall population. (B) Kaplan–Meier curves in women. (C) Kaplan–Meier curves in men. (D) Kaplan–Meier curves in lung cancer. (E) Kaplan–Meier curves in colorectal cancer. (F) Kaplan–Meier curves in gastric cancer. CI, confidence interval; HR, hazard ratio

tients who did not receive curative chemotherapy (HR = 1.491, 95% CI = 1.298–1.713), those with a higher serum total protein level (HR = 1.469, 95% CI = 1.284–1.681) and those with a higher KPS score (HR = 1.453, 95% CI = 1.271–1.662). In contrast, this relationship was attenuated in patients who received curative chemotherapy (HR = 1.041, 95% CI = 0.801–1.353), those with a low serum total protein level (HR = 1.018, 95% CI = 0.797–1.300) and those with a lower KPS score (HR = 1.176, 95% CI = 0.894–1.546) (all $P < 0.05$). Although some effect modifications were observed for other covariates investigated after the stratification analyses, none of them were statistically significant (all $P > 0.05$).

## Discussion

This was a large-scale cohort study that included 5134 patients with cancer cachexia at multiple centres in China. Based on previous evidence from other institutions and our own studies, we hypothesized and subsequently confirmed that the TA provides significant prognostic information about patients with cancer cachexia. To our knowledge, this is the first study that evaluated using such a simple, two-parameter index that integrates information on the fat mass and nutrition for prognostic purposes in Asian populations with cancer cachexia. We demonstrated that the TA effectively reflects the nutritional status, inflammation status, anthropometric status, physical performance and QOL and is significantly associated with multiple short-term clinical outcomes of patients. We also performed parallel comparisons showing that the TA has better discrimination performance to predict all-cause mortality than the TSF or albumin alone, or the HGS, NRI, PNI, CONUT, SII or mGPS in the overall study population. We also derived sex-specific, outcome-oriented TA cutoffs to facilitate its implementation in clinical or primary healthcare settings. We revealed that the TA is independently and robustly associated with the mortality of patients with cancer cachexia. These findings suggest that the TA might be a promising, cost-effective option to help develop better management strategies to optimize the survival outcomes of patients with cancer cachexia. Importantly, this study was conducted in a geographically representative, multicentre cohort, increasing the generalizability of our findings.

The adipose tissue (AT) in the human body is broadly classified as white AT (WAT), which stores triglycerides in the form of lipid droplets, or brown AT (BAT), the main function of which is thermogenesis.[28] The 'browning' of AT (transformation of WAT to BAT) is an important phenotype associated with weight loss and cancer cachexia.[29] Tumours can directly activate thermogenesis[30] through inflammatory mediators such as IL-6, leading to increased lipid mobilization, lipolysis and WAT browning.[31] Because the skin is one of the

**Table 3** Multivariable models of the relationship between the triceps skinfold–albumin index and overall survival

| Models | Overall population, HR (95% CI) | | | | | Sensitivity analysis, HR (95% CI) | |
|---|---|---|---|---|---|---|---|
| | No./deaths | Model 0[a] | Model 1[b] | Model 2[c] | Model 3[d] | No./deaths | Model 4[e] |
| TA, decreasing | 5134/1514 | 1.038 (1.033–1.044) | 1.031 (1.026–1.036) | 1.020 (1.014–1.027) | 1.017 (1.011–1.025) | 4860/1241 | 1.012 (1.005–1.019) |
| Female | 2408/557 | 1.042 (1.033–1.050) | 1.036 (1.028–1.045) | 1.019 (1.009–1.030) | 1.019 (1.008–1.030) | 2314/463 | 1.014 (1.003–1.027) |
| Male | 2726/957 | 1.030 (1.022–1.036) | 1.028 (1.020–1.035) | 1.020 (1.012–1.029) | 1.016 (1.007–1.025) | 2546/778 | 1.010 (1.001–1.019) |
| TA, per 1 SD[f] decreasing | 5134/1514 | 1.742 (1.616–1.876) | 1.567 (1.447–1.695) | 1.344 (1.225–1.475) | 1.292 (1.171–1.427) | 4860/1241 | 1.196 (1.075–1.332) |
| Female | 2408/557 | 1.647 (1.488–1.821) | 1.541 (1.391–1.704) | 1.266 (1.122–1.427) | 1.259 (1.105–1.435) | 2314/463 | 1.190 (1.031–1.374) |
| Male | 2726/957 | 1.587 (1.418–1.776) | 1.550 (1.385–1.739) | 1.381 (1.209–1.577) | 1.292 (1.125–1.486) | 2546/778 | 1.178 (1.014–1.366) |
| TA, low vs. normal[g] | 5134/1514 | 1.859 (1.677–2.062) | 1.724 (1.553–1.915) | 1.446 (1.286–1.625) | 1.381 (1.223–1.560) | 4860/1241 | 1.263 (1.102–1.447) |

Abbreviations: CI, confidence interval; HR, hazard ratio; SD, standard deviation; TA, triceps skinfold–albumin index.
[a]Model 0 is the unadjusted crude model.
[b]Model 1 is adjusted for the age at baseline (continuous) and sex (reference = female).
[c]Model 2 is adjusted for the age at baseline (continuous), sex (reference = female), tumour stage (reference = I), radical surgery (reference = no), curative chemotherapy (reference = no), handgrip strength (continuous), total protein (continuous), the Patient-Generated Subjective Global Assessment score (reference = 0 to 1) and cancer type (reference = lung cancer).
[d]Model 3 is adjusted for all variables in Model 2, plus prealbumin (continuous), calf circumference (continuous), the Nutritional Risk Screening 2002 score (reference = <3), the Karnofsky Performance Status score (continuous) and global quality of life score (continuous).
[e]Model 4 is adjusted for all covariates in Model 3, but excluded the patients who died within the first 3 months after enrolment.
[f]SDs of the TA: overall = 14.6, female = 12.2 and male = 16.0.
[g]TA low, female <49.9 or male <45.6; TA normal, female ≥49.9 or male ≥45.6.

largest organs that store WAT,[32] TSF-reflected subcutaneous WAT loss may be an effective indicator for the onset and severity of both inflammation and cachexia, which impact the prognosis of patients. In accordance with these lines of evidence, a lower TA was associated with indicators of systemic inflammation including the C-reactive protein level and neutrophil-to-lymphocyte ratio in the present study. However, similar patterns of associations between the TSF and biomarkers of systemic inflammation were not observed in the general oncology populations, as described in our previous studies.[15,16] These findings may imply that the TSF is a better prognostic factor in patients with cancer cachexia than in the general oncology population, possibly because it is more related to inflammation, which is a critical factor involved in the development and progression of cancer cachexia. This may also partially explain the comparable prognostic value of the TA and TSF in men (*Table 2*). Because male cancer patients generally have lower TSF values than female cancer patients,[16] they may be more sensitive to the outcome-related fat mass depletion. This assumption is also partially supported by our previous study, which found that men have higher survival-related fat mass index thresholds than women,[17] despite the fact that women generally have higher fat mass storage than men. Interestingly, these findings imply that the prognostic value of the TA may extend beyond the cancer cachexia spectrum. However, due to the limited scope of the present study, future studies will be needed to explore the underlying mechanisms regarding this topic and address the potential applications of the TA in other patient groups.

Albumin is a widely used marker of protein-energy wasting, and its clinical usefulness for indicating the inflammatory process, nutritional status and prognosis of cancer patients has been widely described.[15,17] Albumin is also recommended as a feasible measure of inflammation in the GLIM framework for diagnosing malnutrition[9] and the 2008 framework by Evans et al. for diagnosing cachexia.[33] In addition, albumin is the only component that has been included by the NRI, PNI and CONUT systems for assessing the nutritional status. A recent study showed that the geriatric nutrition risk index (a modified version of the NRI, calculated based on the serum albumin level, and current and historic body weight) is related to inflammation and predicts the prognosis in elderly patients with cancer cachexia.[10] We observed similar results in the present study, indicating that the TA is associated with serum markers of systemic inflammation and significantly predicts the mortality in patients with cancer cachexia. More importantly, we observed that the TA has better discrimination performance in the overall population and in men compared with the NRI (*Table 2*). A multivariable survival analysis in age subgroups also showed that the TA was independently associated with survival in both younger patients (HR = 1.426, 95% CI = 1.186–1.715) and older patients (HR = 1.330, 95% CI = 1.129–1.566), which implies a wider range for applications. Additionally, the NRI includes

| Models | Cases/events | HR (95%CI) adjusted | *P* adjusted | *P* interaction |
|---|---|---|---|---|
| **Overall** | 5134/1514 | 1.381 (1.223-1.560) | <0.001 | |
| ***Age, years*** | | | | 0.357 |
| < 60 | 2841/717 | 1.426 (1.186-1.715) | <0.001 | |
| ≥ 60 | 2293/797 | 1.330 (1.129-1.566) | 0.001 | |
| ***Sex*** | | | | 0.437 |
| Female | 2408/557 | 1.407 (1.142-1.734) | 0.001 | |
| Male | 2726/957 | 1.358 (1.167-1.579) | 0.001 | |
| ***Clinical stage*** | | | | 0.055 |
| I to II | 1684/323 | 1.225 (0.932-1.611) | 0.145 | |
| III to IV | 3450/1191 | 1.457 (1.271-1.670) | <0.001 | |
| ***Radical surgery*** | | | | 0.923 |
| Yes | 2132/466 | 1.364 (1.094-1.700) | 0.006 | |
| No | 3002/1048 | 1.386 (1.197-1.605) | <0.001 | |
| ***Curative chemotherapy*** | | | | 0.033 |
| Yes | 823/374 | 1.041 (0.801-1.353) | 0.766 | |
| No | 4311/1140 | 1.491 (1.298-1.713) | <0.001 | |
| ***Handgrip strength*** | | | | 0.200 |
| Normal | 2606/649 | 1.476 (1.217-1.789) | <0.001 | |
| Low | 2528/865 | 1.335 (1.139-1.564) | <0.001 | |
| ***Calf circumference*** | | | | 0.918 |
| Normal | 1825/440 | 1.282 (0.993-1.656) | 0.056 | |
| Low | 3309/1074 | 1.451 (1.264-1.666) | <0.001 | |
| ***Total protein, g/L*** | | | | 0.019 |
| < 60 | 1018/337 | 1.018 (0.797-1.300) | 0.889 | |
| ≥ 60 | 4116/1177 | 1.469 (1.284-1.681) | <0.001 | |
| ***Prealbumin, mg/L*** | | | | 0.452 |
| < 200 | 2495/898 | 1.448 (1.247-1.682) | <0.001 | |
| ≥ 200 | 2639/616 | 1.188 (0.955-1.479) | 0.122 | |
| ***NRS2002*** | | | | 0.907 |
| < 3 | 1329/301 | 1.321 (0.951-1.836) | 0.097 | |
| ≥ 3 | 3805/1213 | 1.388 (1.215-1.585) | <0.001 | |
| ***PG-SGA*** | | | | 0.852 |
| < 4 | 1190/215 | 1.169 (0.788-1.733) | 0.438 | |
| ≥ 4 | 3944/1299 | 1.404 (1.234-1.597) | <0.001 | |
| ***KPS*** | | | | <0.001 |
| < 80 | 774/289 | 1.176 (0.894-1.546) | 0.248 | |
| ≥ 80 | 4360/1225 | 1.453 (1.271-1.662) | <0.001 | |
| ***Global QOL*** | | | | 0.883 |
| < 80 | 3967/1266 | 1.358 (1.190-1.550) | <0.001 | |
| ≥ 80 | 1167/248 | 1.478 (1.066-2.050) | 0.019 | |
| ***Cancer site*** | | | | 0.967 |
| Lung | 1083/489 | 1.280 (1.031-1.590) | 0.025 | |
| Colorectum | 1078/225 | 1.488 (1.074-2.062) | 0.017 | |
| Stomach | 821/296 | 1.423 (1.085-1.866) | 0.011 | |
| Other GI sites | 799/306 | 1.258 (0.966-1.637) | 0.089 | |
| Breast | 550/42 | 1.236 (0.474-3.223) | 0.665 | |
| Other | 803/156 | 1.295 (0.851-1.970) | 0.228 | |

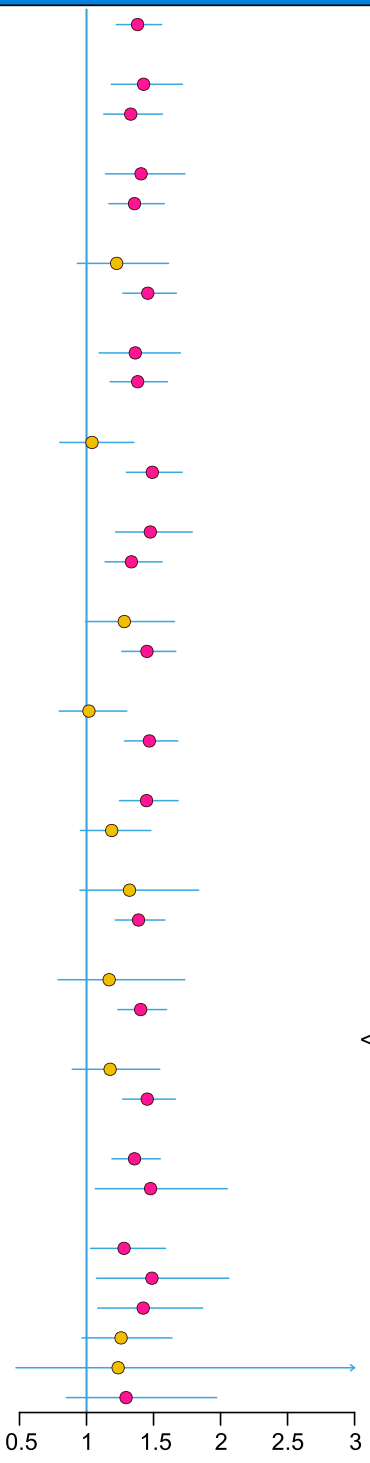


**Figure 5** Subgroup and interaction analysis of the associations of the triceps skinfold–albumin index (TA) with survival. Other gastrointestinal (GI) cancers, including biliary, oesophageal, gastric stromal, liver and pancreatic cancers; other cancers, including lymphoma and bladder, brain, cervical, endometrial, nasopharyngeal and ovarian cancers. CI, confidence interval; HR, hazard ratio; KPS, Karnofsky Performance Status score; NRS2002, Nutritional Risk Screening 2002 score; PG-SGA, Patient-Generated Subjective Global Assessment score; QOL, quality of life score

information on the changes in body weight and data that are often obtained based on patient-reported usual/historic data. These data can be subject to recall bias that can cause instability when calculating the NRI. In contrast, the TSF is a relatively objective parameter that affords greater certainty for the TA during clinical use.

Although HGS was suggested to be an independent prognostic factor in patients with cachexia,[34] its prognostic value in the present study was lower than that of the TA. This finding was similar to a previous study showing that a low fat mass index outperforms handgrip weakness and malnutrition in predicting cancer survival.[17] For other comparators, the PNI,[11] SII[11] and mGPS[35] have all been shown to be related to overall survival of patients with cancer cachexia, and the CONUT significantly predicts progression-free and overall survival in patients with advanced malignancy.[36] However, all of these factors showed lower discrimination performance than the TA in the present study. It has been reported that SAT catabolism and the inflammation status are important indicators of the onset and progression of cachexia.[1,37] The fact that the TA integrates this information might explain why it was superior to other indices that mainly consist of serum parameters. A recent study also found that integration of the BMI and albumin has greater performance in predicting overall survival than 15 other nutrition- or systemic inflammation-based indicators in patients with lung cancer.[24] This supports our approach that integrated both an anthropometric measurement and a serum parameter to develop the TA.

In an exploratory analysis, we included all nine indices to determine how many of them were independent predictors of the OS in the study population. A BIC-based stepwise variable selection showed that only the TA was an independent predictor, and all other indices were excluded (BIC = 24 329.01). Therefore, we did not adjust for other indices in the multivariate Cox regression analysis. Further justifying the removal of these indices is the fact that they all reflect the status of patients (nutritional status and inflammation), and the TA has been suggested to be superior to other indices. It would thus be expected that the exclusion of the other indices would minimize the potential collinearity of the model. This approach was also supported by a recent study that compared the prognostic value of 16 indicators in patients with lung cancer.[24]

The KPS score-associated effect modification in the multivariate Cox regression analysis (*Figure 5*) is noteworthy. In a previous large cohort study that included 12 138 cancer patients, we observed positive associations between a low CC or a low TSF and cancer mortality.[15] Interestingly, these associations were also interacted with the KPS score, similar to what was observed in the present study. However, the mechanisms underlying this phenomenon remain largely unknown. A possible explanation for this finding might be the relatively small sample size of the low KPS score group in the present study ($n$ = 774, events = 289). Notably, the association between a low TA and mortality was only attenuated in the low KPS score group (with the lower limit of the 95% CI crossing the null line), without completely changing direction (where a risk factor would become a protective factor). To test whether the small patient number was responsible for the present observations, we re-dichotomized the KPS score as $\leq$80 versus $>$80 to allocate more patients to the low KPS score group ($n$ = 1856, events = 718) and performed the subgroup Cox regression analysis again. The results showed that the independent associations between the TA and mortality were sustained in both the low KPS score group (HR = 1.358, 95% CI = 1.144–1.613, $P < 0.001$) and the high KPS score group (HR = 1.335, 95% CI = 1.122–1.588, $P < 0.001$). The between-variable interaction also became insignificant in this new analysis ($P$ = 0.146). These findings at least partly support our assumption. Nevertheless, due to the indirectness of this exploratory analysis, future studies employing the original KPS score cutoff with a larger sample size in the low KPS score group are needed to confirm our findings.

This study still has some limitations that must be noted. First, unmeasured confounding factors are possible in all observational studies. However, we comprehensively analysed the baseline data of patients and adjusted the covariates based on both statistical and scientific approaches to minimize this possibility. Second, reverse causality may explain some of the associations we observed in the multivariable survival analysis. However, the results were robust after excluding those patients who died within the first 3 months, which may not completely eliminate, but should partially reduce this probability. Third, the associations between the TA and mortality need further replication in a wider variety of geographical regions, countries and ethnic groups. However, the study population was a large-scale, multicentre cohort that included patients from diverse geographical regions of China and was representative of the general Chinese cancer patients. This strengthens the generalizability of the study results. Fourth, because Asians have anthropometric differences compared with Western populations,[38] the prognostic impact of the TA needs to be re-evaluated when applied in non-Asian patients. Fifth, the TSF may be less accurate than those adiposity parameters derived from more advanced technologies such as dual-energy x-ray absorptiometry, computed tomography and bioelectrical impedance analysis. However, due to its noninvasive, inexpensive and simple nature, the TSF can be used in wider settings, including the primary healthcare facilities and smaller institutions without these advanced technologies. Additionally, its cost-effective nature makes planned, repeated assessment possible, allowing the dynamic changes in the adiposity status during hospitalization to be monitored to enable the development and use of operational surveillance algorithms. Nevertheless, future studies using adiposity parameters derived from more advanced technologies will be needed to replicate our find-

ings. To maximize statistical power, we used bootstrap resampling and cross-validation techniques to obtain unbiased estimates in our study. Future studies with independent external data, especially non-Asian cohort data, are needed to confirm the prognostic value of the TA. However, the present study was conducted in a large, nationwide and geographically representative Chinese cohort. More importantly, studies from another Chinese team,[14] as well as a non-Asian international multicentre study,[39] also confirmed the prognostic value of adipose loss in cancer cachexia. These findings support the proposed use of the index in real-world clinical scenarios.

In conclusion, this study defined and evaluated the prognostic value of a novel index, the TA, which integrates information on the TSF and albumin level. This index effectively reflects the nutritional status, inflammation status, anthropometric status, physical performance and QOL of patients and is significantly associated with multiple short-term clinical outcomes of patients. It also has better discrimination performance to predict the mortality of patients with cancer cachexia than the TSF or albumin alone, the HGS, or the existing NRI, PNI, CONUT, SII and mGPS systems. In addition, the TA is independently and robustly associated with the mortality of patients with cancer cachexia. These findings suggest that the TA might act as a promising, feasible option to help develop better management strategies and provide significant prognostic information for patients with cancer cachexia.

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## Conflicts of interest

The authors declare no conflicts of interest.

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## Ethical statement

The authors certify that the 'Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2021' has been followed.[40] The national and international research ethics guidelines were followed, including the Deontological Code of Ethics and the 1964 Declaration of Helsinki and its later amendments. All patients provide written consent for the use of their data, and this study was approved by the institutional ethics committee of all participating institutions.

## Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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