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Prognostic Significance of C-Reactive Protein–Albumin Score for Cachexia, Severe Malnutrition, and Survival in Patients with Cancer

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Tables 1 to 3 are available in the Supplementary Files section.

Prognostic Significance of C-Reactive Protein–Albumin Score for Cachexia, Severe Malnutrition, and Survival in Patients with Cancer

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Abstract

Background: This study aimed to develop and validate the C-reactive protein-albumin score (CAZ score) using a multicenter cohort, evaluating its prognostic value for cancer patients and its association with severe malnutrition and cachexia.

Methods: The analysis included a multicenter cohort of 6,492 cancer patients, with validation in Cohort A (n = 4,548) and Cohort B (n = 1,944). The CAZ score was calculated by normalizing baseline C-reactive protein and albumin levels into z-scores and combining them, then stratifying into four categories (normal, mild, moderate, severe). Kaplan-Meier analysis, Cox proportional hazards models, and restricted cubic

spline analysis were used to assess the CAZ score's prognostic value for overall survival (OS). Logistic regression examined its associations with severe malnutrition and cancer cachexia, with sensitivity analysis excluding short-term mortality to test robustness.

Results: Kaplan-Meier analysis revealed significant stepwise differences in OS across the four CAZ score categories (71.9% vs 65.9% vs 54.9% vs 42.3%, Log-rank $P < 0.001$). Restricted cubic spline analysis showed a significant linear dose-response relationship between the continuous CAZ score and cancer-related mortality risk ($P < 0.001$). The CAZ score-based inflammatory grading system provided significant prognostic stratification, with substantial differences in OS among patients in different inflammatory burden grade groups (85.5% vs 62.9% vs 46.9%, $P < 0.001$). Cox models identified the CAZ score as an independent prognostic factor for OS, with severe CAZ scores correlating to a 2.102-fold higher mortality risk compared to the normal group (95% CI: 1.872–2.360, $P < 0.001$). Logistic regression demonstrated a dose-dependent increase in the risk of severe malnutrition and cachexia ($P < 0.001$) with higher CAZ scores. All findings were consistently replicated in the two independent validation cohorts.

Conclusion: The CAZ score, a novel standardized composite biomarker, effectively predicts OS in cancer patients and identifies those at high risk for severe malnutrition and cachexia.

Keywords: C-reactive protein - albumin score; Cancer; Overall survival; Prognostic marker; Cachexia; Malnutrition

Introduction

Malignant neoplasms remain a leading global cause of morbidity and mortality, placing a significant and increasing burden on public health systems worldwide. According to the latest global cancer statistics, over 29 million new cancer cases are reported annually, with more than 10.7 million cancer-related deaths each year; these figures are expected to rise further by 2050 due to population growth, aging, and modifiable lifestyle risk factors[1,2]. Despite substantial advancements in oncological care—such as precision diagnostics, multimodal treatment regimens (including surgery, chemotherapy, radiotherapy, targeted therapy, and immune checkpoint inhibitors), and optimized supportive care—overall survival (OS) for many cancer patients, especially those with advanced disease, remains inadequate[3-5]. A major limitation of current clinical prognostic stratification is the overreliance on tumor-node-metastasis (TNM) staging and histopathological features, which primarily reflect tumor-intrinsic biological traits but fail to capture the complex bidirectional interactions between the tumor microenvironment and the host's systemic physiological state, including systemic inflammation, nutritional status, and immune function[6-8]. Therefore, there is a pressing need for novel, practical, and well-validated composite biomarkers that integrate host-derived inflammatory and nutritional parameters to enhance prognostic accuracy and guide personalized cancer management.

Chronic systemic inflammation is widely recognized as a hallmark of cancer progression, driving tumor initiation, local invasion, distant metastasis, and therapeutic resistance through multiple interconnected pathophysiological mechanisms[9,10]. Within the tumor microenvironment, cancer and stromal cells secrete a cascade of pro-inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor-α, and granulocyte-colony stimulating factor), triggering a systemic acute-phase response that disrupts host immune and metabolic homeostasis[11,12]. This persistent inflammatory state not only impairs anti-tumor immune surveillance by inhibiting cytotoxic T cells and natural killer cells but also induces a catabolic metabolic shift, reducing hepatic protein synthesis, increasing skeletal muscle wasting, and causing progressive nutritional depletion[13,14]. Conversely, nutritional imbalance and malnutrition exacerbate systemic inflammation, creating a vicious cycle that accelerates disease progression and worsens clinical outcomes for cancer patients[15,16]. Consequently, inflammatory and nutritional biomarkers have emerged as promising prognostic tools in oncology, with robust clinical evidence linking their expression to OS, treatment response, and adverse clinical events[17-19].

C-reactive protein (CRP) and serum albumin are well-established, routinely measured clinical biomarkers that reflect the core aspects of cancer-related systemic inflammation and nutritional status, respectively[20,21]. CRP, a prototypical acute-phase protein synthesized by the liver in response to pro-inflammatory signaling, serves as a direct and sensitive marker of systemic inflammation, consistently associated with increased tumor aggressiveness, distant metastasis, and poor survival across multiple cancer types[22,23]. Serum albumin, a key indicator of systemic nutritional reserves, also plays critical roles in immune regulation, antioxidant defense, and drug transport. Hypoalbuminemia, in turn, is an independent predictor of treatment intolerance, higher incidence of adverse events, and increased all-cause mortality in cancer patients, reflecting both nutritional depletion and the suppressive effects of chronic inflammation on hepatic protein synthesis[24-26]. While individual CRP or albumin measurements provide independent prognostic value, they fail to capture the integrated effects of the inflammation-nutrition axis. This dynamic interplay between inflammation and nutrition is a major determinant of the host's tolerance to cancer and its treatment.

To address the limitations of single-biomarker assessments, composite inflammatory-nutritional scores (e.g., the CRP/albumin ratio [CAR], Glasgow Prognostic Score [GPS], and modified Nutrition Risk Index) have been developed and explored for prognostic use in cancer patients[27,28]. These composite tools have advanced the integration of inflammatory and nutritional status in cancer prognosis, yet their clinical utility and inter-institutional reproducibility are limited by two key unresolved issues. First, most existing scores lack a standardized calculation framework, resulting in inconsistent application in both clinical and research settings. Second, none of these tools account for interlaboratory variability in the reference ranges and measurement cut-offs for CRP and albumin—an inherent issue in clinical laboratory testing that introduces bias and reduces the comparability of results across

different medical centers[29,30]. These critical technical shortcomings limit the generalizability of current composite scores and highlight the need for a novel, standardized inflammation-nutrition composite index capable of overcoming interlaboratory measurement variability and enabling consistent, objective integration of CRP and albumin for pan-cancer prognostic assessment.

In this study, the CRP–albumin score (CAZ score) is introduced as a novel composite biomarker that quantifies the host's systemic inflammation-nutrition burden by standardizing baseline CRP and albumin levels into z-scores and integrating these normalized values. The z-score standardization is the core innovation of the CAZ score: it calibrates individual CRP and albumin measurements against population-based means and standard deviations, effectively mitigating the impact of interlaboratory reference range variability and enabling a unified, objective assessment of deviations from normal physiological levels. This standardized approach allows for consistent integration of CRP and albumin across clinical centers, providing a significant advantage over existing composite inflammatory-nutritional scores. The study utilized a large, multicenter cohort as the training set, with two independent internal validation cohorts, to comprehensively evaluate the CAZ score in a pan-cancer population. The aims include assessing the association between the CAZ score and OS, validating its independent prognostic value after adjusting for established clinical, demographic, and tumor-related confounders, and exploring the dose-response relationship between the standardized CAZ score and cancer-related all-cause mortality. Additionally, the study investigates the CAZ score's association with severe malnutrition and cancer cachexia in cancer patients, and verifies its prognostic performance across different tumor types and TNM clinical stages.

Materials and Methods

Study Design and Population

This multicenter retrospective cohort study utilized de-identified clinical data from the Investigation on Nutritional Status and Clinical Outcomes of Common Cancers (INSCOC) database (registration number: ChiCTR1800020329). Patients with pathologically or cytologically confirmed malignant tumors diagnosed between January 2012 and December 2021 were screened for eligibility. A total of 6,492 eligible patients were included in the training cohort for the development and optimization of the CAZ score. Two independent internal validation cohorts were established to assess the stability and prognostic value of the CAZ score: validation cohort A (n = 4,548) and validation cohort B (n = 1,944). All cohorts were stratified according to key clinical factors, including tumor type, TNM stage, age, and sex, to ensure baseline comparability and minimize selection bias.

Eligible participants were required to be ≥ 18 years old at the time of cancer diagnosis, have a histopathologically or cytologically confirmed malignant tumor, possess available baseline peripheral blood test results for CRP and serum albumin obtained within 1 week before treatment initiation, and have complete clinical, pathological, and follow-up data, including survival status, treatment regimens, and nutritional assessment indicators. Patients were excluded if they had active acute or

chronic infections or autoimmune diseases at diagnosis, severe hepatic or renal insufficiency (Child–Pugh class C or creatinine clearance < 30 mL/min), were pregnant or lactating, had a hospital stay of < 48 hours after diagnosis with incomplete initial clinical data collection, lacked key follow-up information such as survival time or cause of death, had received immunotherapy or systemic glucocorticoid therapy within 1 month before baseline blood sampling, or had other synchronous or metachronous primary malignant tumors.All participants signed an informed consent form and this study was approved by the Institutional Review Board of The First Affiliated Hospital of Guangxi Medical University (Ethical number: NO.2022-KY-(043)).

Data Collection

Relevant clinical and laboratory data for all enrolled patients were retrospectively extracted from institutional electronic medical record systems and standardized case report forms in the INSCOC database, with rigorous verification and cross-checking procedures to ensure data accuracy and completeness. The collected variables included four main categories: demographic characteristics (age, sex, lifetime smoking history [≥ 100 cigarettes], alcohol consumption [at least once per week], and family history of cancer); clinical characteristics (tumor type [lung, esophageal, gastric, hepatic, intrahepatic bile duct, pancreatic, colorectal, breast, female reproductive, urinary, nasopharyngeal, and central nervous system malignancies], TNM stage according to the 8th edition of the American Joint Committee on Cancer (AJCC) criteria, treatment modalities [surgery, radiotherapy, chemotherapy], length of hospital stay, hospitalization costs, comorbidities such as hypertension and diabetes, Karnofsky Performance Status [KPS] score, 90-day mortality, and survival status); laboratory indicators (baseline CRP and albumin levels, complete blood count parameters [white blood cell, neutrophil, lymphocyte, platelet, and red blood cell counts, as well as hemoglobin concentration], and liver and renal function parameters); and nutritional and complication-related indicators (Patient-Generated Subjective Global Assessment [PG-SGA] score, Nutritional Risk Screening 2002 [NRS2002] score, and clinically diagnosed cancer cachexia status).

CAZ score calculation

The CAZ score was derived by summing the Z-values of CRP and albumin. The specific steps were as follows: (1) Calculate the mean (μ) and standard deviation (σ) for each indicator: For the baseline data of all included patients, the mean CRP value was 19.63 mg/L with a standard deviation of 41.12, and the mean albumin value was 38.81 g/L with a standard deviation of 5.56; (2) Calculate the Z-value for each indicator using the formula: Z-value = (individual indicator value - mean) / standard deviation; (3) CAZ score = CRP $^{\text{Z-value}}$ - albumin $^{\text{Z-value}}$; (4) Score classification: divided into quartiles—normal (lowest quartile), mild (second quartile), moderate (third quartile), and severe (highest quartile). For each biomarker, the Z-value was calculated according to the following formula:

$$z\text{-}score=\frac{Individual\ value\text{-}Population\ mean\ (\mu)}{Population\ standard\ deviation(\sigma)}$$

Follow-up and Outcomes

All patients were followed through outpatient visits, telephone interviews, and electronic medical records using a standardized protocol. Follow-up was conducted every 3 months during the first 2 years, every 6 months from years 3–5, and annually thereafter until June 2025.

The primary outcome was OS, defined as the time from cancer diagnosis to death from any cause or last follow-up. Secondary outcomes included nutritional status assessed by the PG-SGA, cancer cachexia defined according to international criteria, and 90-day all-cause mortality.

Statistical Methods

Statistical analyses were performed using R (version 4.3.1), with a two-sided $P < 0.05$ considered significant. Continuous variables were expressed as mean ± SD or median (IQR), and categorical variables as n (%). Kaplan–Meier curves and Log-rank tests compared OS across CAZ score groups. Cox proportional hazards models estimated hazard ratio (HR) and 95% confidence interval (CI), using three models (crude, partially adjusted, and fully adjusted) to assess independent prognostic value. Restricted cubic spline (RCS) analysis evaluated dose–response relationships, and stratified Cox analyses were conducted by tumor type and TNM stage. External validation was performed using two independent cohorts. Logistic regression assessed associations between the CAZ score and severe malnutrition and cachexia. Sensitivity analyses excluding deaths within 6 months were conducted to confirm robustness.

Results

Baseline Characteristics

The study design of this study is shown in **Figure S1**. A total of 6,492 cancer patients were included in the training cohort (mean age 59.44 ± 11.21 years; 60.4% male). The most common tumor types were lung (31.8%), colorectal (19.9%), and gastric cancer (15.4%), with 45.5% of patients at TNM stage IV. Comorbidities included hypertension (20.3%) and diabetes (10.3%), while 47.4% had a smoking history and 23.0% reported alcohol consumption. The incidence of cancer cachexia was 33.9%, with 90-day adverse outcomes in 6.4% and all-cause mortality in 41.3% **(Table S1)**. Patients were stratified by CAZ score into four groups (n = 1,623 each), showing significant stepwise differences across baseline characteristics. Higher CAZ scores were associated with older age, higher male proportion, increased prevalence of comorbidities and unhealthy lifestyle factors, and a greater proportion of advanced-stage disease. Tumor distribution varied across groups, with higher CAZ scores linked to increased proportions of lung, pancreatic, and central nervous system tumors. Laboratory and nutritional parameters progressively deteriorated with increasing CAZ scores, including lower albumin, higher CRP, elevated white blood cell and neutrophil counts, and reduced lymphocyte and hemoglobin levels. Nutritional risk scores (PG-SGA, NRS2002) and cachexia prevalence increased significantly. Clinical outcomes worsened accordingly, with higher CAZ scores associated with increased 90-day adverse events, mortality, length of hospitalization, and healthcare costs ($P < 0.001$).

Tumor Inflammatory Grading System based on CAZ score

Based on the CAZ score data from the enrolled patients, the systemic inflammatory burden was analyzed across 11 common malignant tumors, including lung cancer, gastric cancer, and colorectal cancer. Using the median CAZ score of colorectal cancer as a reference benchmark and considering the overall distribution of CAZ scores across different tumor types, a novel CAZ score-based tumor inflammatory grading system was constructed to quantify the systemic inflammatory burden levels in various cancer types **(Figure S4)**. This grading system stratified the 11 malignancies into three groups based on the degree of inflammatory burden: (1) Mild inflammation group: This group included breast cancer and nasopharyngeal cancer, with median CAZ scores significantly lower than the colorectal cancer reference value, indicating a low systemic inflammatory burden; (2) Moderate inflammation group: This group comprised esophageal cancer, gastric cancer, liver and intrahepatic bile duct cancer, urologic cancer, and female gynecological cancer, with median CAZ scores close to the colorectal cancer reference value, reflecting a moderate level of systemic inflammation; (3) Severe inflammation group: This group included lung and bronchial cancer, pancreatic cancer, and brain and nervous system tumors, with median CAZ scores significantly higher than the colorectal cancer reference value, representing the highest systemic inflammatory burden. To assess the clinical prognostic value of this inflammatory grading system, Kaplan-Meier survival analysis was performed across the different inflammatory grade groups. The results showed that the CAZ score-based tumor inflammatory grading system provided significant prognostic stratification, with highly significant differences in OS among the groups ($P < 0.001$) **(Figure S5)**. Specifically, patients in the mild inflammation group had the highest 5-year OS rate of 85.5%, while those in the moderate inflammation group had a secondary rate of 62.9%. In contrast, patients in the severe inflammation group had the poorest prognosis, with a 5-year OS rate of only 46.9%, and the survival curves exhibited significant differences between the three groups. These findings confirmed that systemic inflammatory burden levels vary inherently across tumor types and are closely associated with the long-term prognosis of cancer patients: higher inflammatory burden correlates with worse survival outcomes.

Kaplan-Meier survival curves of CAZ score

The survival curves showed a clear stepwise decline in OS with increasing CAZ scores, and the OS difference across all four subgroups was statistically significant (Log-rank $P < 0.001$) **(Figure 1)**. Specifically, the 5-year OS rate was highest in the normal CAZ score group (71.9%), followed by the mild group (65.9%), moderate group (54.9%), and severe group (42.3%). The survival gap between the normal and severe groups was substantial, with patients in the severe CAZ score group experiencing nearly a 30% lower 5-year survival rate compared to those with normal scores, indicating a strong association between elevated systemic inflammatory-nutritional burden and poorer survival outcomes. Subgroup analysis by TNM stage revealed that the CAZ score effectively stratified prognosis across all clinical stages, with progressively worse outcomes as the CAZ score increased. This survival

stratification effect was particularly pronounced in advanced-stage (TNM IV) patients **(Figure S2)**. In various tumor types, an increase in CAZ score was linked to a higher risk of death, with higher CAZ scores consistently associated with shorter OS. The survival stratification effect was especially evident in aggressive tumor types, such as lung and gastric cancer **(Figure S3)**.

The relationship between CAZ score and OS

To examine the association between the CAZ score and OS in cancer patients, RCS analysis and Cox proportional hazards regression models were applied, with hierarchical covariate adjustment to validate the robustness of the findings. RCS analysis was initially performed to explore the dose-response relationship between the continuous CAZ score and the risk of all-cause mortality. Consistent significant non-linear associations were observed across all three adjustment models (all *P* for non-linearity < 0.001). As the CAZ score increased from normal to severe ranges, the risk of death demonstrated a continuous and steady upward trend. In the unadjusted model (model a), each 1-point increase in the CAZ score was associated with a 42.6% higher risk of death (HR = 1.426, 95% CI: 1.373–1.480, $P < 0.001$) **(Figure 2A)**. After partial covariate adjustment (model b: age, sex, TNM stage, and tumor type), the predictive efficacy remained robust, with each 1-point increase in the CAZ score linked to a 32.5% higher risk of adverse prognosis (HR = 1.325, 95% CI: 1.272–1.380, $P < 0.001$) **(Figure 2B)**. Even in the fully adjusted model (model c: further adjusted for treatment modalities, comorbidities including hypertension and diabetes, smoking status, alcohol consumption, and family history of cancer), the independent prognostic value of the CAZ score persisted: each 1-point increase was associated with a 30.7% higher mortality risk (HR = 1.307, 95% CI: 1.255–1.362, $P < 0.001$) **(Figure 2C)**. Cox proportional hazards regression analysis further quantified survival differences across CAZ score subgroups (normal, mild, moderate, severe), using the normal group as the reference. After full covariate adjustment, the adjusted HRs for the mild, moderate, and severe CAZ score groups compared to the normal group were 1.208 (95% CI: 1.067–1.369, $P = 0.003$), 1.478 (95% CI: 1.313–1.665, $P < 0.001$), and 2.102 (95% CI: 1.872–2.360, $P < 0.001$), respectively **(Table 1)**. This indicated that patients with severe CAZ scores had more than double the mortality risk of those with normal scores, demonstrating a strong graded association between higher CAZ scores and poorer survival outcomes.

To mitigate potential bias from early mortality (which may confound the association between the CAZ score and long-term OS), a sensitivity analysis was conducted by excluding 415 patients who died within 6 months of follow-up. Repeating the Cox regression analysis in the remaining population confirmed the stability of the findings. After full covariate adjustment, the adjusted HRs for the mild, moderate, and severe CAZ score groups (vs. normal group) were 1.223 (95% CI: 1.074–1.392, $P = 0.002$), 1.443 (95% CI: 1.273–1.635, $P < 0.001$), and 1.806 (95% CI: 1.593–2.047, $P < 0.001$), respectively **(Table S2)**.

The relationship between CAZ score and severe malnutrition

Logistic regression analyses showed a dose-dependent association between the

CAZ score and severe malnutrition, with the normal group as reference. In the crude model, mild, moderate, and severe CAZ groups had progressively higher risks (OR = 1.263, 95% CI: 1.046–1.524, $P = 0.015$). After adjustment for age, sex, TNM stage, and tumor type, the association for the mild group was attenuated and became non-significant (OR = 1.162, 95% CI: 0.957–1.411, $P = 0.130$), whereas the moderate and severe groups remained significantly associated ($P < 0.001$).In the fully adjusted model, the association persisted for moderate and severe CAZ groups, with adjusted ORs of 1.928 (95% CI: 1.604–2.318) and 4.163 (95% CI: 3.479–4.981), respectively ($P < 0.001$), indicating nearly twofold and over fourfold increased risks of severe malnutrition. No significant association was observed for the mild group (OR = 1.161, ,95% CI: 0.955–1.410, $P = 0.133$) **(Table 2)**.

The relationship between CAZ score and cachexia

Logistic regression analyses revealed a dose-dependent association between CAZ scores and cancer cachexia, using the normal group as reference. In the crude model (model a), the mild subgroup showed no significant increase in cachexia risk (OR = 1.108, 95% CI: 0.946–1.297, $P = 0.203$), while moderate and severe subgroups had significantly elevated risks (P < 0.001).After partial adjustment (model b), the mild subgroup remained non-significant (OR = 1.047, 95% CI: 0.887–1.237, $P = 0.588$), whereas moderate and severe subgroups retained significant associations (OR = 1.418 and 2.307, $P < 0.001$). In the fully adjusted model (model c), the association persisted for moderate and severe subgroups, with adjusted OR of 1.430 (95% CI: 1.213–1.685) and 2.332 (95% CI: 1.980–2.746), respectively (P < 0.001). No significant association was observed for the mild subgroup (OR = 1.046, 95% CI: 0.885–1.236, $P = 0.600$) **(Table 3)**.

Randomized Internal Validation

To validate the stability and generalizability of the CAZ score's prognostic value, a randomized internal validation was conducted by dividing the entire study population into a training cohort (cohort A, $n = 4548$) and a validation cohort (cohort B, $n = 1944$) at a 7:3 ratio using computer-generated random numbers. Consistent methodological strategies were applied to both cohorts for outcome assessment. The baseline characteristics of the two cohorts were highly similar, with no statistically significant differences in key clinical and demographic indicators (all $P > 0.05$) **(Table S3)**. Kaplan-Meier survival analysis revealed a consistent stepwise decrease in OS with increasing CAZ scores in cohort A. The 5-year OS rates for the normal, mild, moderate, and severe CAZ score groups were 70.5%, 66.1%, 55.3%, and 40.9%, respectively, with statistically significant differences across subgroups (Log-rank $P < 0.001$) **(Figure 3A)**. A similar trend was observed in cohort B, where prognosis worsened progressively with elevated CAZ scores, with 5-year OS rates of 75.3%, 65.3%, 53.8%, and 45.6% for the normal, mild, moderate, and severe groups, respectively **(Figure 3B)**. Multivariate Cox proportional hazards regression analysis further confirmed the independent prognostic value of the CAZ score. In cohort A, compared to the normal group, the mild, moderate, and severe CAZ score groups exhibited elevated HR for OS, with HR of 1.144 (95% CI: 0.987–1.327, $P = 0.075$),

1.394 (95% CI: 1.212–1.604, $P < 0.001$), and 2.126 (95% CI: 1.856–2.436, $P < 0.001$), respectively **(Table S4)**. Consistent findings were observed in cohort B, where the mild, moderate, and severe CAZ score groups also showed significantly worse OS compared to the normal group, with corresponding HR of 1.365 (95% CI: 1.082–1.723, $P = 0.009$), 1.752 (95% CI: 1.397–2.197, $P < 0.001$), and 2.104 (95% CI: 1.682–2.632, $P < 0.001$), respectively **(Table S5)**.

Discussion

This study introduces the CAZ score, a novel composite biomarker developed for the first time in this research, and validates its role as an independent prognostic indicator for cancer patients. By integrating systemic inflammatory and nutritional status through standardized z-score transformation, the CAZ score addresses critical limitations of existing biomarkers such as the GPS and the CAR. These existing scores lack unified calculation frameworks and fail to account for interlaboratory variability, whereas the CAZ score provides a practical and consistent tool for clinical risk stratification and personalized management[27,28]. Its strong association with OS, severe malnutrition, and cancer cachexia highlights the pivotal role of the interplay between inflammatory burden and nutritional balance in influencing cancer outcomes. Its novelty lies in overcoming long-standing challenges in pan-cancer prognostic assessment.

The prognostic value of the CAZ score lies in its ability to capture the bidirectional crosstalk between chronic inflammation and nutritional depletion—two key features of cancer progression—while addressing technical shortcomings in previous composite indices[31]. Chronic systemic inflammation[32-34], reflected by elevated CRP levels, drives tumor progression through multiple mechanisms, including promoting cell proliferation, invasion, and angiogenesis, while also suppressing anti-tumor immune responses[35]. Conversely, reduced serum albumin levels indicate impaired hepatic protein synthesis and metabolic imbalance[36-38], which are consequences of both nutritional insufficiency and the inhibitory effects of inflammation on anabolic processes[39]. Unlike existing composite scores, the CAZ score's unique approach of z-score normalization calibrates individual measurements against population benchmarks, a method that effectively harmonizes heterogeneous biomarker data across studies and ensures consistent application across clinical centers. This innovation, central to the CAZ score development, enables a more comprehensive assessment of the host's systemic response to cancer than single biomarkers or traditional composite tools. It aligns with the growing understanding that cancer prognosis depends not only on tumor-intrinsic factors but also on the host's capacity to tolerate the disease and its treatment.

The strong dose-dependent relationships observed between the CAZ score and both survival outcomes and nutritional complications highlight the clinical relevance of this newly developed indicator beyond prognostic stratification. The score's association with severe malnutrition and cachexia—two conditions driven by inflammatory mediators that induce catabolic metabolism and muscle wasting—suggests that it can serve as an effective screening tool to identify patients at high risk of nutritional deterioration. Early identification of such patients could facilitate timely

interventions, including nutritional support and anti-inflammatory strategies, to interrupt the vicious cycle of inflammation-induced catabolism and nutritional depletion. This translational potential addresses an unmet clinical need, as current nutritional screening tools often fail to integrate inflammatory status and may not fully capture the systemic burden of cancer— a gap that the CAZ score, as the first developed composite, is uniquely positioned to fill.

The development of a tumor inflammatory grading system based on the CAZ score further extends the novel insights of this research. This grading system, derived from the first-of-its-kind score, reveals inherent differences in systemic inflammatory burden across common malignancies, with more aggressive tumor types exhibiting higher inflammatory loads and poorer survival outcomes. Such findings highlight the biological heterogeneity of cancer and suggest that inflammatory profiles may serve as a unifying feature linking tumor biology to clinical outcomes. The grading system also provides a framework for tailoring management strategies, as patients with high-inflammatory-burden tumors may benefit from more intensive supportive care or targeted anti-inflammatory therapies alongside standard treatment— a practical application enabled by the CAZ score's initial development.

Several strengths of the study enhance the credibility and generalizability of the findings related to this newly developed score. The large multicenter cohort, combined with rigorous random internal validation, ensures that the CAZ score's prognostic performance is consistent across diverse patient populations. The standardized z-score calculation— a key innovation of its first-time development— eliminates the impact of interlaboratory variability in reference ranges, a critical technical advantage that enhances the score's applicability across clinical settings. Additionally, the comprehensive adjustment for demographic, clinical, and tumor-related confounders strengthens the evidence for the CAZ score's independent prognostic value, reinforcing the significance of its initial development.

Despite these strengths, certain limitations should be acknowledged. The retrospective design of the study means that dynamic changes in the CAZ score during treatment could not be monitored, leaving unanswered questions about how score fluctuations might influence prognosis or response to intervention—questions that future research on this newly developed indicator should address. Additionally, some potential confounding factors related to treatment details or prior medical history were not fully captured in the analysis, which may have influenced the observed associations. The slightly inconsistent prognostic performance in the smaller validation cohort also suggests that larger studies may be needed to confirm the CAZ score's stability across all patient subgroups.

Future research should address these limitations by conducting prospective studies to evaluate dynamic changes in the CAZ score and their association with treatment response and long-term outcomes. Interventional trials are also necessary to determine whether targeting patients with high CAZ scores—the first composite indicator integrating standardized inflammation and nutrition metrics—through nutritional and anti-inflammatory interventions can improve survival and quality of life. Further

validation in diverse populations, including those with rare tumors or those receiving novel therapies such as immunotherapy, would enhance the generalizability of this newly developed score. Additionally, exploring the biological mechanisms underlying the CAZ score's prognostic value could uncover new therapeutic targets, such as specific inflammatory pathways or metabolic regulators, which could be modulated to improve outcomes—thus advancing the translational impact of this initial development.

Conclusion

The CAZ score, developed in this study, serves as an independent prognostic factor for OS in cancer patients. It is closely associated with severe malnutrition and cachexia, offering a standardized, practical tool for clinical risk stratification and enabling early targeted interventions to improve patient outcomes.

Declaration

Human Ethics and Consent to participate

This study was conducted in accordance with the Helsinki Declaration. All participants signed an informed consent form and this study was approved by the Institutional Review Board of The First Affiliated Hospital of Guangxi Medical University (Ethical number: NO.2022-KY-(043)). The study was approved by the INSCOC's institutional review board (Name of the ethic committee: Medical Ethics Committee of First Affiliated Hospital of Sun yat-sen University; Registration number: ChiCTR1800020329; Registration Date: December 24, 2018; Registration website: http://www.chictr.org.cn)

Consent to publish

Not applicable.

Availability of data and materials

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Declaration of competing interests

There are no competing interests.

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Author contributions

NX: Draft writing, Data collection, Data analysis, Investigation, Methodology, Validation. CX: Software, Methodology, Supervision. LW: Formal analysis, Methodology. SW: Formal analysis, Methodology. YC: Data organization, Writing – review & editing. SL: Data collection, Formal analysis. CC: Data curation, Formal analysis, Investigation. CJ: Data collection, Formal analysis. ZY: Formal analysis, Methodology. TC: Data curation, Investigation. HS: Review and editing, Supervision, Conceptualization. HL: Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing, Funding acquisition, Resources.

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doi:10.1177/15353702221087962

Figure Legend

Figure 1. Kaplan-Meier curve of cancer patients with different levels of CAZ score.

Figure 2. Dose-response relationship between CAZ score and survival in patients with cancer.

Notes:

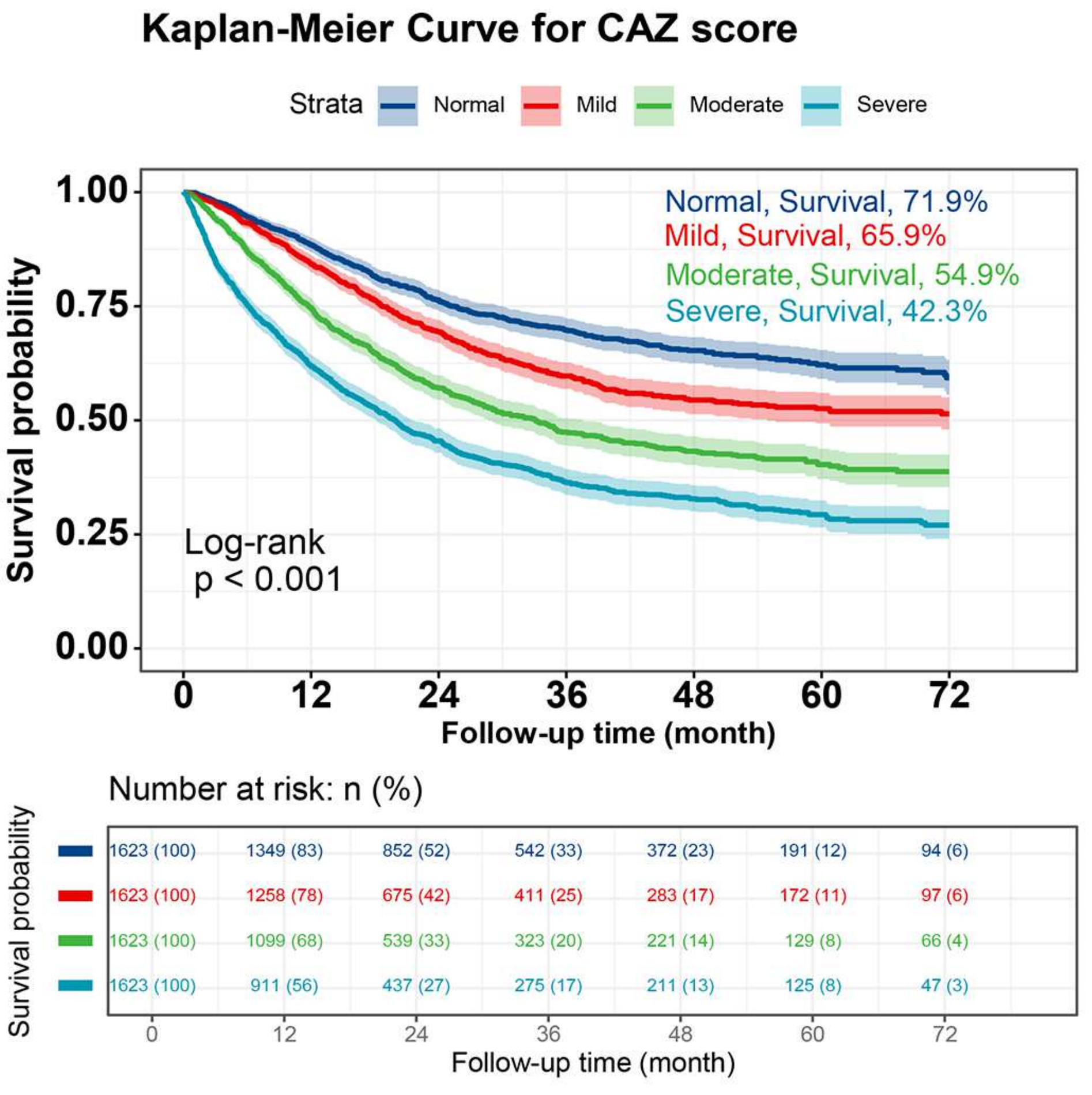
Model a: No adjusted.

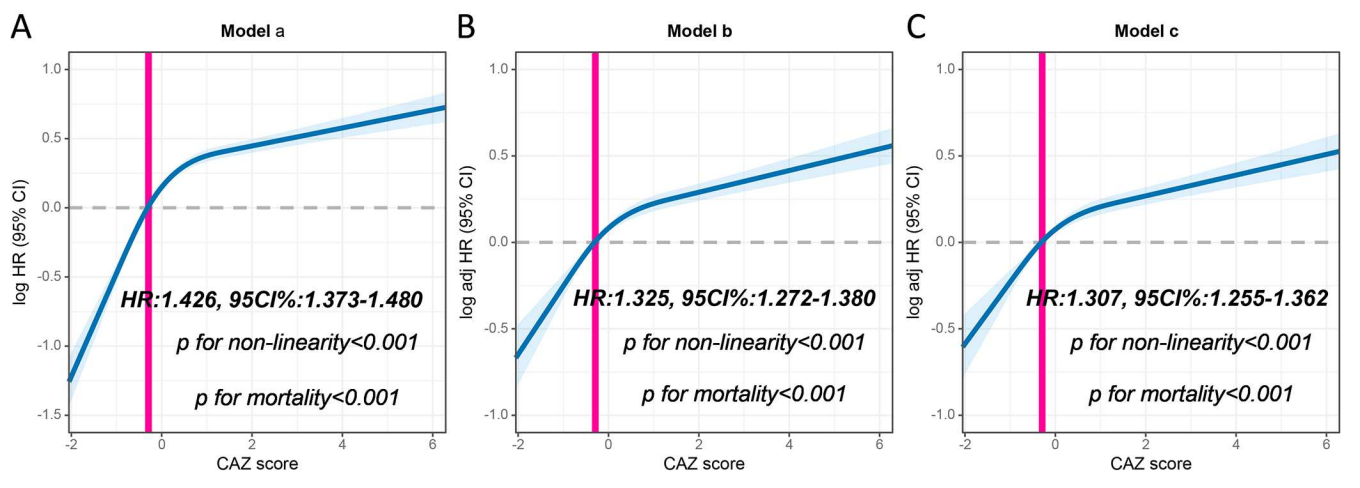
Model b: Adjusted for age, sex, TNM stage, tumor types.

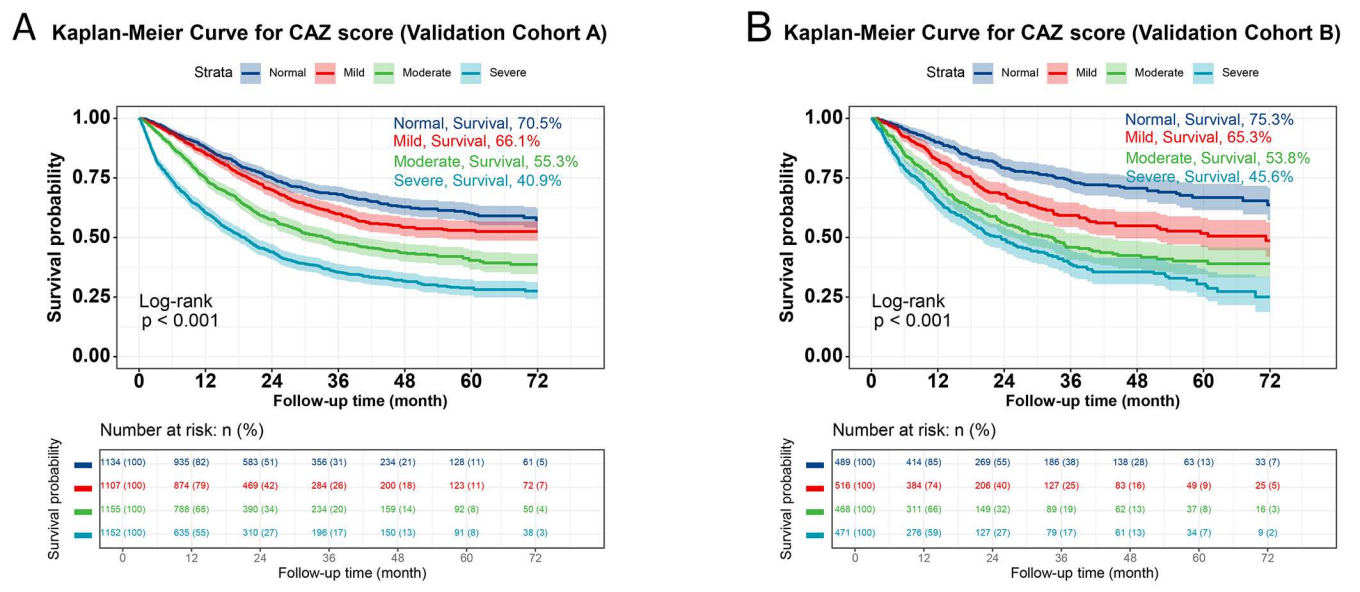
Model c: Adjusted for age, sex, TNM stage, tumor types, surgery, radiotherapy, chemotherapy, hypertension, diabetes, smoking, drinking, family history.

Figure 3. Validation of Kaplan-Meier curve of CAZ score in patients with cancer.

Notes: A, Validation cohort A; B, Validation cohort B.


Kaplan-Meier Curve for CAZ score
Strata
Normal
Mild
Moderate
Severe
Survival probability
1.00
0.75
0.50
0.25
0.00
Normal, Survival, 71.9%
Mild, Survival, 65.9%
Moderate, Survival, 54.9%
Severe, Survival, 42.3%
Log-rank
p < 0.001
0
12
24
36
48
60
72
Follow-up time (month)
Number at risk: n (%)
1623 (100) 1349 (83) 852 (52) 542 (33) 372 (23) 191 (12) 94 (6)
1623 (100) 1258 (78) 675 (42) 411 (25) 283 (17) 172 (11) 97 (6)
1623 (100) 1099 (68) 539 (33) 323 (20) 221 (14) 129 (8) 66 (4)
1623 (100) 911 (56) 437 (27) 275 (17) 211 (13) 125 (8) 47 (3)
Survival probability
0
12
24
36
48
60
72
Follow-up time (month)


A
Model a
log HR (95% CI)
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2
0
2
4
6
CAZ score
HR:1.426, 95CI%:1.373-1.480
p for non-linearity<0.001
p for mortality<0.001
B
Model b
log adj HR (95% CI)
1.0
0.5
0.0
-0.5
-1.0
-2
0
2
4
6
CAZ score
HR:1.325, 95CI%:1.272-1.380
p for non-linearity<0.001
p for mortality<0.001
C
Model c
log adj HR (95% CI)
1.0
0.5
0.0
-0.5
-1.0
-2
0
2
4
6
CAZ score
HR:1.307, 95CI%:1.255-1.362
p for non-linearity<0.001
p for mortality<0.001


A
Kaplan-Meier Curve for CAZ score (Validation Cohort A)
Strata
Normal
Mild
Moderate
Severe
Normal, Survival, 70.5%
Mild, Survival, 66.1%
Moderate, Survival, 55.3%
Severe, Survival, 40.9%
Survival probability
1.00
0.75
0.50
0.25
0.00
Log-rank
p < 0.001
0
12
24
36
48
60
72
Follow-up time (month)
Number at risk: n (%)
Survival probability
1134 (100) 935 (82) 583 (51) 356 (31) 234 (21) 128 (11) 61 (5)
1107 (100) 874 (79) 469 (42) 284 (26) 200 (18) 123 (11) 72 (7)
1155 (100) 788 (68) 390 (34) 234 (20) 159 (14) 92 (8) 50 (4)
1152 (100) 635 (55) 310 (27) 196 (17) 150 (13) 91 (8) 38 (3)
0 12 24 36 48 60 72
Follow-up time (month)
B
Kaplan-Meier Curve for CAZ score (Validation Cohort B)
Strata
Normal
Mild
Moderate
Severe
Normal, Survival, 75.3%
Mild, Survival, 65.3%
Moderate, Survival, 53.8%
Severe, Survival, 45.6%
Survival probability
1.00
0.75
0.50
0.25
0.00
Log-rank
p < 0.001
0
12
24
36
48
60
72
Follow-up time (month)
Number at risk: n (%)
Survival probability
489 (100) 414 (85) 269 (55) 186 (38) 138 (28) 63 (13) 33 (7)
516 (100) 384 (74) 206 (40) 127 (25) 83 (16) 49 (9) 25 (5)
468 (100) 311 (66) 149 (32) 89 (19) 62 (13) 37 (8) 16 (3)
471 (100) 276 (59) 127 (27) 79 (17) 61 (13) 34 (7) 9 (2)
0 12 24 36 48 60 72
Follow-up time (month)

Supplementary Files

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- Table2.docx
- supplementarymaterial.docx