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C-reactive protein-triglyceride-glucose index and its obesity-related derivatives as predictors of cardiovascular incidence and cause-specific mortality among cancer survivors: a prospective cohort study

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Abstract

Background

The C-reactive protein–triglyceride glucose index (CTI), an innovative composite marker for evaluating metabolic-inflammatory dysregulation, remains unclear in its clinical utility among cancer survivors. This study aims to evaluate the associations of CTI and its obesity-related derivatives with cardiovascular disease (CVD) risk, stroke events, heart failure events, all-cause mortality, and CVD-related mortality in cancer survivors.

Methods

This prospective cohort study was conducted using data from the UK Biobank. Participants were categorized according to quartiles of CTI-related indices. Univariate and multivariate Cox regression models, along with restricted cubic splines (RCS), were used to evaluate the associations between CTI-related indices and all five study endpoints. Predictive performance was assessed using receiver operating characteristic (ROC) curves, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). Sensitivity and subgroup analyses were performed to evaluate the robustness of the findings.

Results

Among cancer survivors, high CTI-related indices were significantly and positively associated with incident CVD events (HR 1.65 [1.44–1.89]), heart failure events (HR 2.28 [1.81–2.87]), all-cause mortality (HR 1.54 [1.38–1.71]), and CVD-related mortality (HR 3.71 [1.77–7.79]). Adding CTI-related indices, particularly CTI-WHtR, to a basic demographic model significantly improved the prediction of these outcomes. Notably, the association between CTI-WHtR and all-cause mortality was more pronounced in participants aged < 60 years, females, never-smokers, and those without hypertension. Moreover, no evident association was observed between CTI-WHtR and cardiovascular-disease-specific mortality among participants receiving oral anticoagulant therapy.

Conclusion

Elevated CTI-related indices were significantly associated with a higher risk of cardiovascular events. CTI-WHtR may serve as a simple accessible marker for stratifying the future risk of CVD events in cancer survivors.

Introduction

The number of people living with a history of cancer is rising because of a growing and aging population as well as advancements in early detection and treatment that have improved survival. On January 1, 2025, about 18.6 million people with a history of cancer are living in the United States, and this number is projected to exceed 22 million by 2035[1]. Compared with cancer-related deaths, non-cancer causes now emerged as the leading mortality driver in most solid tumors, with CVD as primary contributors[2, 3]. Cancer survivors carry a persistently elevated lifetime risk of CVD and CVD-specific death relative to the general population[4, 5]; the excess hazard is detectable from the day of diagnosis and is most pronounced among survivors of typically good-prognosis tumors such as breast, prostate and bladder cancer[5–7].Thus, the prevention of CVD is a central pillar of long-term cancer survivorship care.

Insulin resistance (IR), characterized by diminished insulin sensitivity that impairs glucose uptake and produces chronic hyperglycemia[8, 9], is a central pathophysiological driver of cardiovascular disease by activating inflammatory responses, inducing oxidative stress and causing metabolic dysregulation[8, 10, 11]. In recent years, the triglyceride-glucose (TyG) index has emerged as a convenient marker for predicting IR and has been shown to serve as a simple surrogate marker for the risk stratification of future CVD events in cancer survivors[12–15]. Meanwhile, systemic inflammation—classically reflected by C-reactive protein (CRP)—further accelerates atherogenesis independently of metabolic dysfunction[16, 17]. Consequently, the CTI was constructed to integrate information on glycaemia, lipid metabolism and systemic inflammatory activity[18]; elevated CTI values are subsequently and independently associated with higher risks of cancer-related cachexia, population-level cancer mortality and incident cardiovascular events[11, 19, 20]. However, the relationship between CTI—along with its obesity-related derivatives, including CTI-body mass index (CTI-BMI), CTI-waist circumference (CTI-WC) and CTI-waist-to-height ratio (CTI-WHtR)—and cardiovascular disease risk in the high-risk population of cancer survivors remains unknown.

To address these critical research gaps, we leveraged comprehensive prospective cohort data from the UK Biobank to investigate the associations of the CTI and its obesity-related derivatives with incident cardiovascular events, stroke events, heart failure events, all-cause mortality and CVD-related mortality among cancer survivors. Our findings may inform targeted preventive strategies and personalized risk assessment in this high-risk population.

Methods

Study design and study population

This prospective study was conducted utilizing the UK Biobank database[21]. Established between 2006 and 2010, this extensive population-centric cohort enrolled more than 500,000 individuals aged 37–73 years across England, Wales, and Scotland. Assessment procedures encompassed the collection of biological specimens, comprehensive physiological evaluations, and self-reported demographic or clinical data via touchscreen surveys. Participants gave written informed consent permitting the linkage of their health profiles to national hospital admission records, cancer registries, and death registries.

Ethical clearance for the overall UK Biobank initiative was granted by the National Health Service (NHS) National Research Ethics Service. The present analysis was authorized by the UK Biobank Access Management Team under Application #332912, alongside supplementary ethical monitoring by the relevant Institutional Review Board and the National Institutes of Health.

A comprehensive flowchart detailing the participant selection process is provided in **Fig.S1**. The initial study population comprised 24,645 cancer survivors. Baseline cancer diagnoses were ascertained via the 10th Revision of the International Classification of Diseases (ICD-10) codes by linking to national registries, specifically the Hospital Episode Statistics and the National Cancer Registration and Analysis Service. To qualify as a survivor, individuals must have a documented hospitalization for malignancy (ICD codes C00–C97) alongside subsequent health screening assessments.

Subsequent exclusions were applied sequentially to establish the final dataset. We first omitted individuals with prevalent cardiovascular disease at baseline or those missing CVD-related information (n = 2,014). To ensure the accurate derivation of the CTI and its associated obesity metrics, we further excluded subjects lacking essential biomarker or anthropometric records. This included missing data for C-reactive protein, triglycerides, or glucose (n = 3,745); body mass index (n = 59); waist circumference (n = 37); and standing height (n = 50). A final exclusion step removed participants with incomplete covariate measurements (n = 1,545). Consequently, the remaining sample eligible for the primary evaluation consisted of 17,270 cancer survivors.

Assessment of CTI, CTI-BMI, CTI-WC and CTI-WHtR

The concentrations of fasting plasma glucose, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were quantified via a Beckman Coulter AU5800 auto-analyzer in accordance with uniform laboratory guidelines. After collection, blood specimens underwent immediate processing to isolate serum and plasma fractions, which were subsequently cryopreserved at -80°C prior to formal analysis. Comprehensive descriptions of the assay methodologies and internal quality assurance protocols can be accessed via the official UK Biobank documentation (Reference ID: 1227). The formulas for calculating CTI, CTI-BMI, CTI-WC, CTI-WHtR were as follows[18, 22, 23]:

1. CTI = 0.412 × Ln (CRP [mg/L]) + Ln (TG [mg/dl] × FPG [mg/dl])/2;
2. CTI-BMI = CTI × BMI, and BMI = weight (kg)/height^2 (m^2);
3. CTI-WC = CTI × WC (cm);
4. CTI-WHtR = CTI × WHtR, and WHtR = WC (cm)/height (cm);

Definition of outcomes

The primary outcome in our analysis was the incidence of cardiovascular disease events, defined as a composite endpoint consisting of CVD, stroke, and heart failure. Incident cases (including disease status and initial diagnosis date) were identified using ICD-10 codes: CVD (I20-I25), stroke (I60, I61, I63, I64),

and heart failure (I50, I11.0, I13.0, and I13.2). For CVD-related mortality, we obtained information from official death registries. We extracted the underlying cause of death (Field ID 40001, ICD-10 coded) and date of death (Field ID 40000), following established criteria from previous studies.

We calculated the time-to-event for disease incidence as the time from baseline assessment to the date of first diagnosis, while the time to CVD-related mortality was measured from enrollment until death. For participants without events, censoring occurred at the last follow-up date or the date of loss to follow-up. These records were linked with national death registries, including NHS Digital for England and Wales (data complete as of May 30, 2024) and the National Records of Scotland (data complete as of December 31, 2023), ensuring comprehensive mortality ascertainment.

Assessments of covariates

A comprehensive set of baseline covariates was extracted to adjust for potential confounding in our analysis. Demographic and lifestyle characteristics consisted of age, genetic sex (male or female), and self-reported ethnicity (categorized as White or non-White). We also recorded the specific assessment center (England, Scotland, or Wales). Educational background was classified into standard UK categories, ranging from College/University degrees to A levels, O levels, CSEs, NVQ/HNC, or other professional qualifications. Furthermore, smoking status (never, previous, or current) and alcohol consumption (less than versus at least three times weekly) were documented. Socioeconomic status was assessed by the Townsend Deprivation Index, which was categorized into tertiles, representing low (T1), moderate (T2), and high (T3) deprivation levels. Clinical covariates included a documented history of diabetes mellitus and hypertension. We also accounted for the baseline use of oral anticoagulants (classified as yes or no), which we identified from the baseline self-reported medication records[24]. Laboratory data included baseline lipid profiles, specifically high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).

Statistical analysis

Baseline profiles were summarized using means and standard deviations (SD) for continuous data, and percentages (%) for categorical metrics. To evaluate differences across groups, we applied analysis of variance (ANOVA) for continuous measures and chi-square tests for categorical parameters. We applied Cox proportional hazards regression models to investigate the associations of the CTI and its obesity-adjusted indices with the prespecified outcomes, including total CVD events, stroke, heart failure, all-cause mortality, and CVD-related mortality. The proportional hazards assumption was checked using Schoenfeld residuals. If the assumption was violated, time-varying covariates were introduced into the models to address the non-proportionality. Multicollinearity among the covariates was evaluated through the variance inflation factor (VIF), with a threshold of less than 10 considered acceptable (**Table S1**). Three Cox models were applied. Model 1 was unadjusted. Model 2 was adjusted for age, sex, education attainment, Townsend deprivation index and assessment centre. Model 3 was further adjusted for smoking status, alcohol consumption, hypertension, diabetes mellitus, anticoagulant use, HDL and LDL.

To explore potential nonlinear relationships between CTI, CTI-BMI, CTI-WC, CTI-WHtR and CVD risk, RCS regression was employed.

Kaplan-Meier analysis was performed to assess the cumulative incidence of outcomes, and the log-rank test was applied to compare differences across groups. ROC curves were constructed to assess predictive performance of CTI-related indices for CVD risk, quantified by area under the curve (AUC) values. To estimate the additional predictive power, the NRI and IDI were calculated.

We conducted extensive subgroup analyses to evaluate the robustness of our findings and examine potential effect modifiers. Participants were stratified by key demographic and clinical characteristics, including age (< 60 vs. ≥60 years), genetic sex (male vs. female), ethnicity (white vs. non-white), smoking status (yes vs. no), alcohol consumption (yes vs. No), hypertension (yes vs. no), diabetes mellitus (yes vs. no), and anticoagulant use (yes vs. no). Statistical differences between subgroups were assessed using interaction terms. We further performed sensitivity analyses in cohorts that excluded participants who experienced outcome events within one year and within two years of recruitment, respectively.

All statistical analyses were performed using R version 4.4.1 (R Foundation for Statistical Computing), with two-sided tests and significance threshold of $p < 0.05$.

Results

Baseline characteristics

A total of 17,270 participants were enrolled in this study. Over a median follow-up period of 176 months, 2,659 participants progressed to CVD, 634 developed strokes, and 909 developed heart failure. During the same observation period, 4,099 deaths occurred, of which 173 were adjudicated as CVD-related mortality. The baseline characteristics of study participants stratified by CTI quartiles were displayed in Table 1. The cohort had a median age of 62.0 years (interquartile range [IQR]: 56.0–66.0), with a female predominance (60.2%). In terms of ethnicity, the majority of participants were White (97.6%). Regarding educational attainment, 30.1% of participants held a university or higher degree, whereas 21.3% reported no formal qualifications. The median Townsend Deprivation Index was − 2.29 (interquartile range [IQR]: -3.70–0.19), reflecting overall low levels of deprivation. Current smoking was reported by 8.6% of participants, whereas 91.6% had a history of alcohol consumption. Across increasing CTI quartiles, LDL-C progressively increased, whereas HDL-C levels declined in a step-wise fashion. In addition, patients in the higher CTI quartiles exhibited a higher prevalence of diabetes mellitus and hypertension and were more likely to receive anticoagulant therapy.

Table 1
Baseline characteristics of the participants classified by CTI

Characteristic	Overall N = 17,270	CTI_Q1 N = 4,318	CTI_Q2 N = 4,317	CTI_Q3 N = 4,317	CTI_Q4 N = 4,318	p-value[1]
Age, Median (Q1, Q3)	62.00 (56.00, 66.00)	60.00 (53.00, 65.00)	62.00 (57.00, 66.00)	63.00 (58.00, 66.00)	62.00 (58.00, 66.00)	< 0.001
Genetic sex, n (%)						< 0.001
Female	10,392 (60%)	2,997 (69%)	2,580 (60%)	2,463 (57%)	2,352 (54%)	
Male	6,878 (40%)	1,321 (31%)	1,737 (40%)	1,854 (43%)	1,966 (46%)	
Townsend Deprivation Index, Median (Q1, Q3)	-2.29 (-3.70, 0.19)	-2.39 (-3.75, -0.14)	-2.39 (-3.79, -0.08)	-2.26 (-3.70, 0.25)	-2.05 (-3.59, 0.73)	< 0.001
Qualifications, n (%)						< 0.001
College or University degree	5,196 (30%)	1,651 (38%)	1,340 (31%)	1,196 (28%)	1,009 (23%)	
NVQ or HND or HNC or equivalent	2,322 (13%)	530 (12%)	594 (14%)	594 (14%)	604 (14%)	
Other prof. qual. eg: nursing, teaching	2,287 (13%)	571 (13%)	581 (13%)	581 (13%)	554 (13%)	
A levels/AS levels or equivalent	872 (5.0%)	243 (5.6%)	232 (5.4%)	190 (4.4%)	207 (4.8%)	
CSE or equivalent	2,923 (17%)	725 (17%)	701 (16%)	730 (17%)	767 (18%)	
None of the above	3,670 (21%)	598 (14%)	869 (20%)	1,026 (24%)	1,177 (27%)	
Ethnicity, n (%)						0.048
Non white	417 (2.4%)	127 (2.9%)	104 (2.4%)	97 (2.2%)	89 (2.1%)	
White	16,853 (98%)	4,191 (97%)	4,213 (98%)	4,220 (98%)	4,229 (98%)	
Centre attending, n (%)						0.076

[1]Pearson's Chi-squared test; Kruskal-Wallis rank sum test

Characteristic	Overall N = 17,270	CTI_Q1 N = 4,318	CTI_Q2 N = 4,317	CTI_Q3 N = 4,317	CTI_Q4 N = 4,318	p-value[1]
England	15,199 (88%)	3,809 (88%)	3,827 (89%)	3,800 (88%)	3,763 (87%)	
Scotland	1,222 (7.1%)	321 (7.4%)	291 (6.7%)	302 (7.0%)	308 (7.1%)	
Wales	849 (4.9%)	188 (4.4%)	199 (4.6%)	215 (5.0%)	247 (5.7%)	
Hypertension, n (%)	10,436 (60%)	1,956 (45%)	2,539 (59%)	2,878 (67%)	3,063 (71%)	< 0.001
Diabetes mellitus, n (%)	946 (5.5%)	96 (2.2%)	158 (3.7%)	227 (5.3%)	465 (11%)	< 0.001
Smoking status, n (%)						< 0.001
Current	1,485 (8.6%)	278 (6.4%)	296 (6.9%)	404 (9.4%)	507 (12%)	
Never	8,891 (51%)	2,518 (58%)	2,294 (53%)	2,162 (50%)	1,917 (44%)	
Previous	6,894 (40%)	1,522 (35%)	1,727 (40%)	1,751 (41%)	1,894 (44%)	
Alcohol consumption, n (%)						< 0.001
< 3 times per week	4,084 (24%)	872 (20%)	956 (22%)	1,065 (25%)	1,191 (28%)	
≥ 3 times per week	11,742 (68%)	3,161 (73%)	3,047 (71%)	2,859 (66%)	2,675 (62%)	
Never	1,444 (8.4%)	285 (6.6%)	314 (7.3%)	393 (9.1%)	452 (10%)	
Anticoagulant use, n (%)	2,105 (12%)	401 (9.3%)	490 (11%)	562 (13%)	652 (15%)	< 0.001
HDL, Median (Q1, Q3)	1.42 (1.20, 1.71)	1.68 (1.43, 1.96)	1.49 (1.28, 1.75)	1.36 (1.17, 1.59)	1.22 (1.05, 1.42)	< 0.001
LDL, Median (Q1, Q3)	3.56 (2.98, 4.19)	3.30 (2.82, 3.85)	3.57 (3.01, 4.15)	3.68 (3.07, 4.32)	3.75 (3.10, 4.41)	< 0.001

[1]Pearson's Chi-squared test; Kruskal-Wallis rank sum test

Associations of CTI and its obesity-related derivatives with CVD, stroke, and heart failure

First, the associations of each CTI-related index with the risk of incident CVD, stroke, and heart failure were examined separately. Kaplan–Meier survival curves demonstrated that participants with high CTI, CTI-BMI, CTI-WC and CTI-WHtR exhibited a significantly higher cumulative incidence of these outcomes (all log-rank $P < 0.001$) (Fig. 2A-C; **Fig.S2-S4**). These findings were corroborated by Cox regression models. After fully adjustment for all covariates, Participants with high CTI-related indices exhibited a significantly elevated risk of incident CVD compared with those with low levels, and a similar conclusion was reached in the analysis of heart failure (Fig. 3A; **Fig.S5B; Table S2&S4**). However, formal comparisons based on quartiles showed no statistically significant differences in stroke risk across CTI quartiles. This null finding was consistently observed for all other CTI indices (CTI-WC, CTI-BMI, and CTI-WHtR) as well (**Fig.S5A; Table S3**). Additionally, RCS analysis demonstrated that CTI had a positive linear association with CVD risk (P overall < 0.001, P nonlinear = 0.380); while CTI-BMI, CTI-WC, and CTI-WHtR exhibited positive nonlinear relationships with CVD risk (P overall < 0.05, P nonlinear < 0.05) (Fig. 3D). Similar patterns were observed in the analysis of heart failure risk (**Fig.S6B**). Regarding stroke risk, RCS analysis indicated that only the CTI-WHtR index exhibited a positive linear association relationship with incident stroke (P overall = 0.025, P nonlinear = 0.115) (**Fig.S6A**).

Associations of CTI and its obesity-related derivatives with all-cause mortality and CVD-related mortality

Similarly, the relationships between each CTI-related index and both all-cause mortality and CVD-specific mortality were assessed. Kaplan–Meier analyses showed that elevated CTI, CTI-BMI, CTI-WC, and CTI-WHtR were all associated with significantly higher cumulative rates of all-cause and CVD-specific death (all log-rank $P < 0.001$) (Fig. 2D**&E; Fig.S2-S4**). Cox regression further revealed that higher CTI-related indices were independently associated with both poorer overall survival and a greater rate of cardiovascular death (Fig. 3B-C; **Table S5&S6**). Furthermore, RCS analyses revealed that CTI-WC and CTI-WHtR exhibited a positive linear association with all-cause mortality, whereas CTI and CTI-BMI showed a positive nonlinear relationship (Fig. 4A). For CVD-related mortality, only CTI-WHtR demonstrated a positive nonlinear association, while the remaining CTI-related indices were positively and linearly associated (Fig. 4B).

Predictive performance of CTI and its obesity-related derivatives for outcomes

The predictive performance of CTI-derived indices for outcomes, including total CVD events, stroke, heart failure, all-cause mortality, and CVD-related mortality, was evaluated through ROC curve analysis, NRI, and IDI. When CTI and its obesity-related derivatives were sequentially added to the base model for individual evaluation, CTI-BMI, CTI-WC, and CTI-WHtR conferred significant AUC improvement for all five

study endpoints. In contrast, CTI itself improved the AUC only for the prediction of incident CVD, all-cause mortality, and CVD-related mortality (P < 0.05 by DeLong's test) (Fig. 5). Additionally, CTI-WHtR demonstrated the greatest improvement in reclassification performance for total CVD events, stroke, heart failure, and all-cause mortality, whereas its NRI for CVD-related mortality was marginally inferior to that of CTI-BMI (**Table S7-S11**). For integrated discrimination improvement, CTI-WHtR produced the most substantial IDI gains across all five endpoints (**Table S7-S11**). These results indicate that, compared with traditional risk factors, CTI-related indices—especially CTI-WHtR—offered better predictive value for cardiovascular events in cancer survivors.

Figure 5. Receiver operating characteristic curves for total CVD events (A), stroke events (B), heart failure events (C), all-cause mortality (D), and CVD-related mortality (E) in cancer survivors. The basic model was adjusted for age, genetic sex, ethnicity, socioeconomic status, educational attainment, assessment centre, smoking status, alcohol consumption, HBA1c, HDL-C and LDL-C.

* indicates significantly improved predictive performance versus the basic model by DeLong's test (p < 0.05)

Subgroup and Sensitivity analysis

Subgroup analyses were performed to further assess the association between CTI-WHtR and all five endpoints stratified by age, genetic sex, ethnicity, smoking status, alcohol consumption, hypertension, diabetes mellitus and anticoagulant use. The results showed that the positive linear association between CTI-WHtR and all-cause mortality among cancer survivors was more pronounced in individuals under 60 years old, women, never-smokers, and participants without hypertension (**Table S12-S17**). Interestingly, the positive nonlinear relationship between CTI-WHtR and CVD-related mortality appeared to be abrogated among participants receiving oral anticoagulant therapy (**Table S19**). No additional significant interactions were observed across other subgroups (all P-interaction > 0.05) (**Table S12-S19**). To verify the robustness of our findings, we conducted sensitivity analyses after sequentially excluding individuals with less than one year and less than two years of follow-up. Both sensitivity analyses yielded conclusions consistent with the primary outcomes (**Table S20-S21**).

Discussion

The significant increase in cancer survivorship has brought forth a new clinical challenge: the long-term management of competing risks, especially CVD, heart failure, and stroke [4, 25]. Although traditional risk factors play a role, the cardiotoxic effects of anticancer therapies and the unique metabolic consequences of cancer itself result in a risk profile that is different from that of the general population [26–28]. Consequently, conventional CVD risk scores often underestimate this threat in oncology patients, creating an urgent need for specialized prediction tools [29]. The CTI represents a novel tool that captures the interplay between metabolism and inflammation—key pathways in cardio-oncology; however, its prognostic value specifically within the cancer survivor population remains unquantified [18]. We launched this investigation to translate the theoretical promise of the CTI into validated

prognostic insights for this patient population. Building upon previous research on the TyG index—in which we have already explored the predictive utility of TyG and its obesity-adjusted derivatives (TyG-BMI, TyG-WC, TyG-WHtR) in cancer patients (manuscript under review)—we further incorporated the same anthropometric parameters (BMI, WC, WHtR) to refine the CTI [30].

The Kaplan-Meier analysis illustrated that the associations between CTI and CTI-derived and the cumulative incidence of all three cardiovascular outcomes were statistically significant (all log-rank $P < 0.001$), with clear separation of survival curves across quartiles, supporting the utility of these indices for risk stratification. Subsequent multivariable Cox regression models confirmed that patients with higher CTI values had significantly increased risks of composite CVD. However, when examining heart failure and stroke specifically, the Cox models showed no statistically significant differences in risk across the Q1-Q4 quartiles of any CTI index. We therefore employed restricted cubic spline models to explore the continuous relationship between these indices and event risks. For composite CVD risk, the baseline CTI showed a positive linear association, whereas CTI-WHtR showed a near-linear positive association. Regarding heart failure risk, CTI, CTI-BMI, and CTI-WC all demonstrated positive linear associations. In contrast, none of the CTI indices showed a significant linear association with incident stroke. This finding diverges from previous studies conducted in general populations, which consistently reported positive correlations between CTI and both stroke and heart failure risk. Interestingly, Huo et al. declared in a study that they found no association between the CTI and stroke risk in participants with diabetes, implying that potential influencing factors like metabolic comorbidities exist and could influence the predictive value of CTI for stroke [22]. Given that many cancer survivors receive treatments that can induce or exacerbate metabolic syndrome, such treatment-related metabolic alterations might have obscured a potential association between CTI and stroke in our cohort [31, 32]. Besides, the absolute numbers of stroke and heart failure events were significantly lower than those of composite CVD events, which resulted in limited statistical power for these specific endpoints. Due to this constraint and the consequent uncertainty in the findings, subsequent analyses of disease-specific mortality and subgroup effects focused solely on composite CVD, while stroke and heart failure were not further investigated.

Subsequently, we evaluated the associations of CTI and its related indices with overall survival and CVD-specific mortality. The Kaplan-Meier analyses demonstrated a progressively increasing trend in the cumulative incidence of all-cause and CVD-specific mortality across Q1-Q4 for all CTI-derived indices. Adjusted Cox regression models substantiated these trends. Subsequent restricted cubic spline analyses revealed a positive linear association of CTI-WC and CTI-WHtR with all-cause mortality. At the same time, only CTI-WHtR exhibited a linear relationship with CVD-specific mortality. To further compare the predictive performance of the four indices, we constructed ROC curves for CVD, stroke, and heart failure risk, as well as for all-cause and CVD-specific mortality. The analysis revealed that CTI-WHtR had the highest AUC among the metrics evaluated. This indicates its strong capability to predict long-term heart issues and related deaths in cancer survivors. Research indicates that WHtR is more effective than BMI and WC in assessing cardiovascular risk [33–35]. Although WC directly measures abdominal obesity, its interpretation is influenced by age and sex, often requiring specific adjustments [36, 37]. Although WC directly measures abdominal obesity, its interpretation is influenced by age and sex, often

requiring specific adjustments [34, 38]. In contrast, WHtR not only accurately reflects central obesity but also remains relatively stable across age and sex groups without the need for extensive normalization [34]. Considering the established link between central obesity and cardiovascular risk, it seems both logical and reasonable that CTI-WHtR is more effective at predicting cardiovascular events and CVD-specific mortality in this population [35, 39, 40].

Given CTI-WHtR's superior predictive performance for cardiovascular event risk and CVD-specific mortality, we conducted subgroup and sensitivity analyses to validate its clinical utility further. Subgroup analyses revealed that CTI-WHtR showed better predictive efficacy of all-cause mortality in cancer survivors who were younger than 60 years, female, non-smokers, or without a history of hypertension. For CVD-specific mortality, its predictive capacity was more pronounced in patients without a history of anticoagulant use. The observed interactions are physiologically plausible. Smoking and hypertension are well-established risk factors for mortality, with studies suggesting that their detrimental effects may be amplified in females [41, 42].The superior risk stratification by CTI-WHtR in patients under 60 years highlights the particular importance of monitoring metabolic-inflammatory health in younger cancer survivors [20]. Regarding the modifying effect of anticoagulant use, while direct evidence linking anticoagulants to insulin resistance or metabolic syndrome is limited, some literature suggests that anticoagulants may potentially ameliorate cardiovascular dysfunction in the early stages of metabolic syndrome [43]. Therefore, the pronounced protective effect of anticoagulation on CVD-specific mortality might have attenuated the predictive power of CTI-WHtR in that subgroup. This intriguing finding raises a clinically relevant hypothesis: whether it is feasible to consider performing routine anticoagulant treatment among cancer survivors with elevated CTI-WHtR scores to decrease long-term risk of CVD-related death, even if they have no conventional indications for anticoagulant therapy.

Nonetheless, our study has some limitations. First, CTI and its related indices were calculated at baseline and treated as static; changes in behavior or clinical metrics over time were not captured. Second, the number of deaths related to heart failure and stroke among cancer survivors was quite limited; therefore, the relations of CTI-related indices to disease-specific survival needs further exploration. Additionally, the study was only based on participants' data acquired from the UK Biobank. Therefore, other large-scale cohorts are still needed for further validation.

Conclusion

This prospective study in a large cohort of cancer survivors demonstrated that elevated CTI-related indices (CTI, CTI-BMI, CTI-WC, and CTI-WHtR) were strongly associated with an increased risk of total CVD events, heart failure events, all-cause mortality, and CVD-related mortality. Adding CTI-related indices, particularly CTI-WHtR, to a basic demographic model significantly improved the prediction of these outcomes. Notably, among participants receiving oral anticoagulant therapy, no evident associations were observed between CTI-WHtR indices and CVD-related mortality. These findings hold important public health relevance and offer enhanced methods for future cardiovascular risk assessment among cancer survivors.

Declarations

Availability of data and materials

The data that support the findings of this study are available from the UK Biobank project site, subject to registration and the application process. Data can be found at https://www.ukbio bank.ac.uk.

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Contributions

RHT and SHL designed the study. JYW acquired data and performed statistical analyses. HRW and ZHZ assisted in figure plotting. RHT, SHL and ZHZ drafted the initial manuscript. HMH, ML, JYL, NY and JYW reviewed the manuscript. All authors have read and approved the final submitted version of the manuscript.

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Ethics declarations

Ethics approval and consent to participate

The UKB study was approved by the North West Multi-Centre Research Ethics Committee (11/NW/0382), with all participants providing written informed consent. Conducted in accordance with the Declaration of Helsinki, the research utilized UK Biobank data under application number 332192.

Competing interests

The authors declare no competing interests.

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Figures

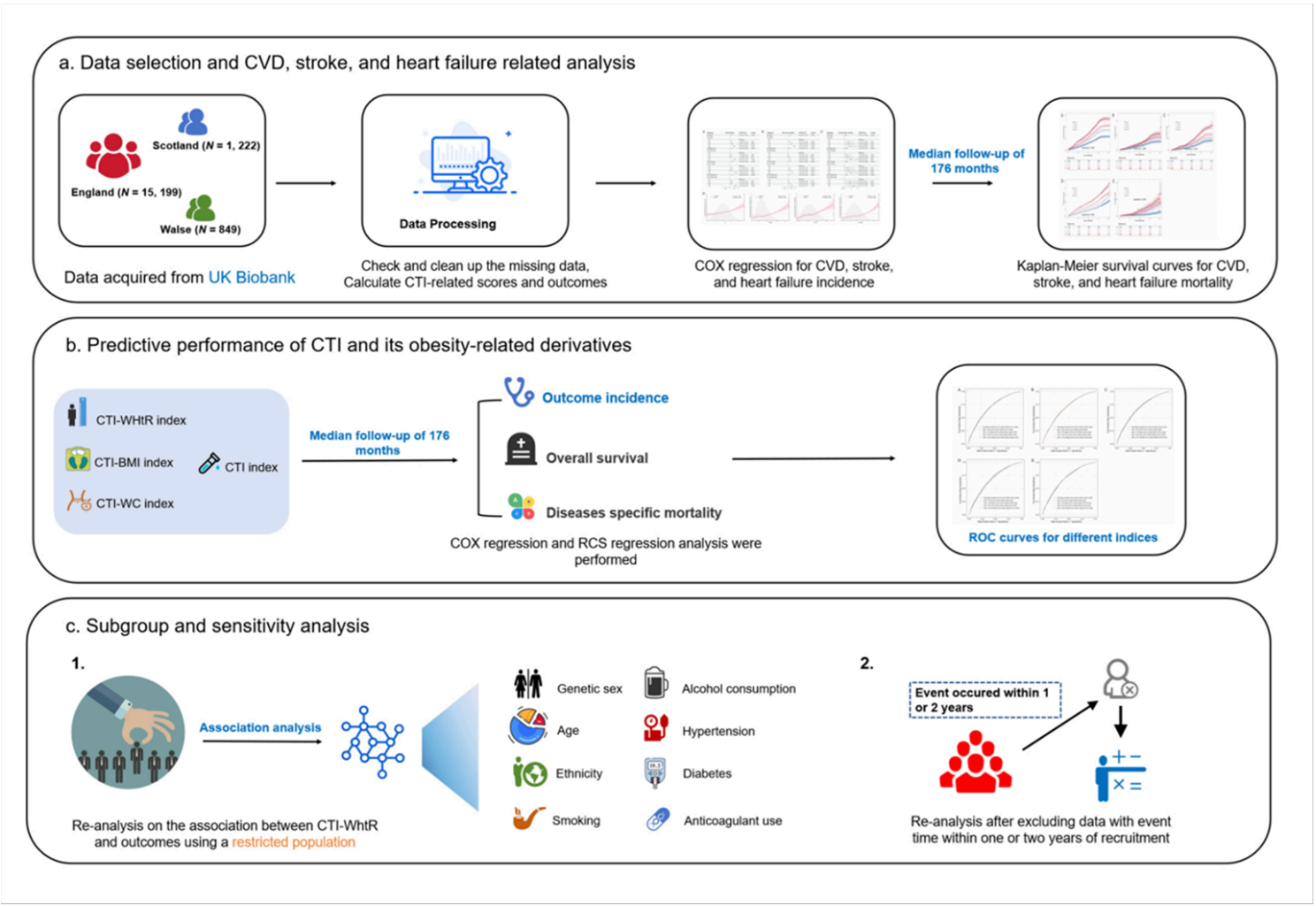


Figure 1

Graphical Abstract

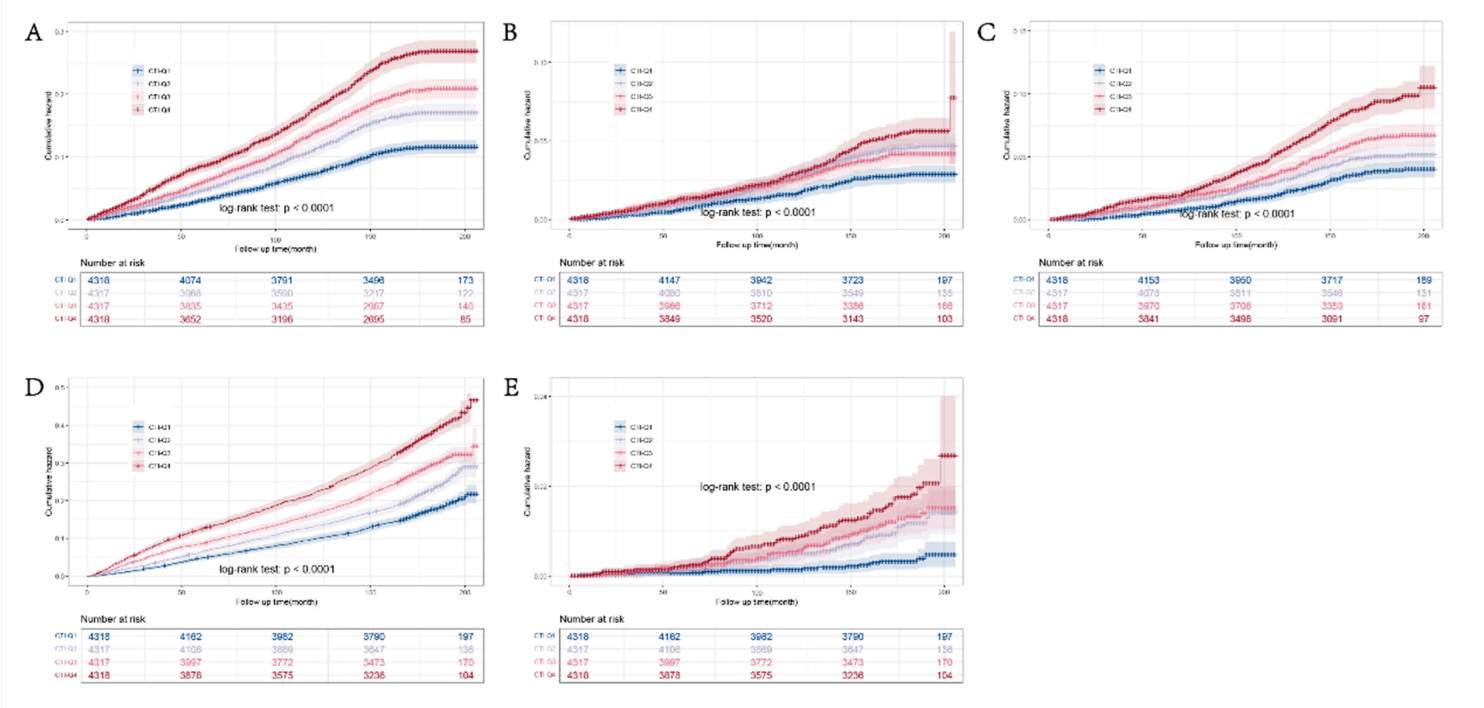


Figure 2

Kaplan-Meier plots of outcomes by CTI quartiles. (A) Associations of CTI and incidence CVD. (B) Associations of CTI and incidence stroke. (C) Associations of CTI and incidence heart failure. (D) Associations of CTI and all-cause mortality. (E) Associations of CTI and CVD-related mortality.

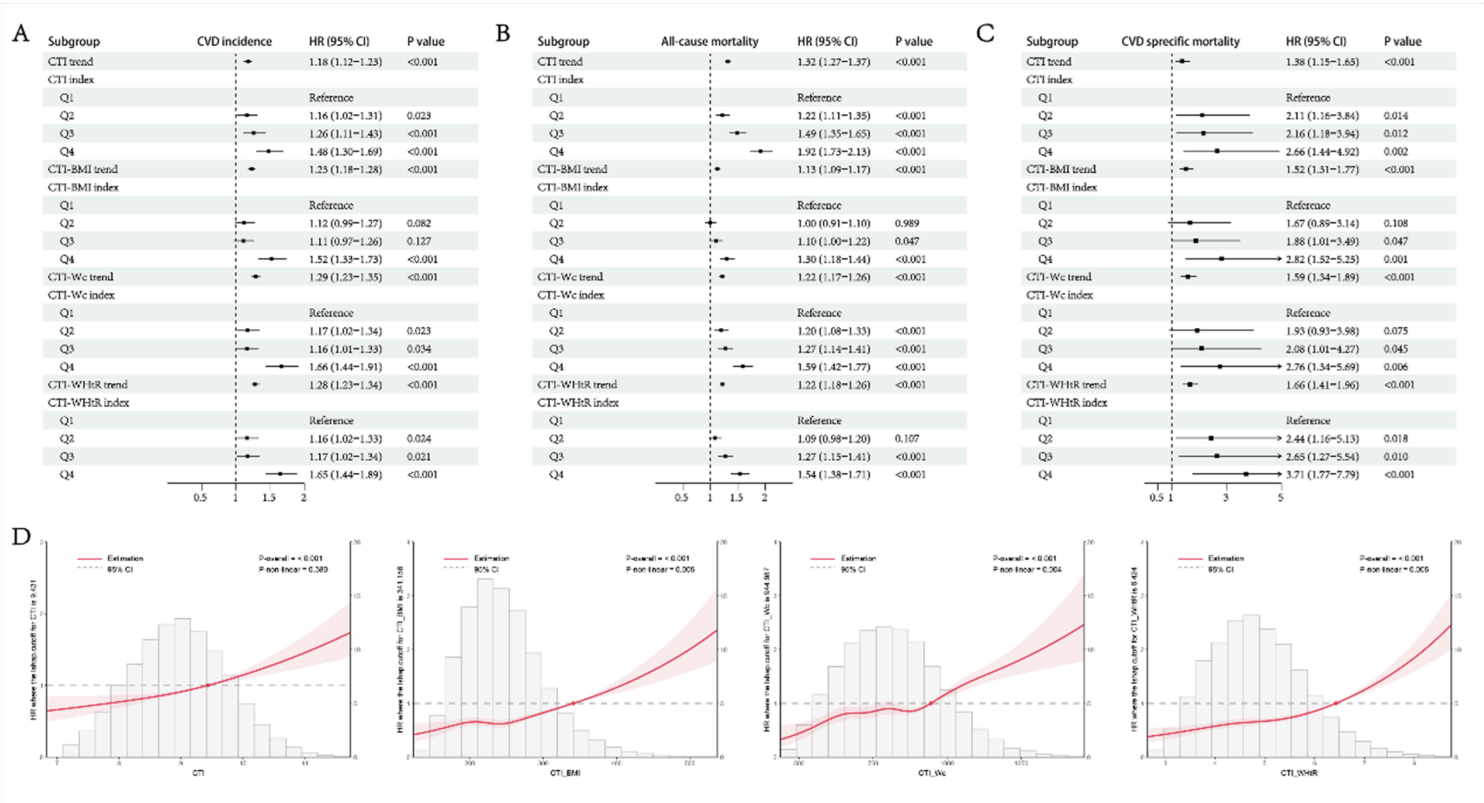


Figure 3

Forest plot of CTI and its obesity-related derivatives in relation to total CVD events (A), all-cause mortality (B), and CVD-related mortality (C) using fully adjusted Cox proportional hazards model. Associations between CTI and its obesity-related derivatives with total CVD events (D) evaluated by RCS after fully adjustment for the covariates.

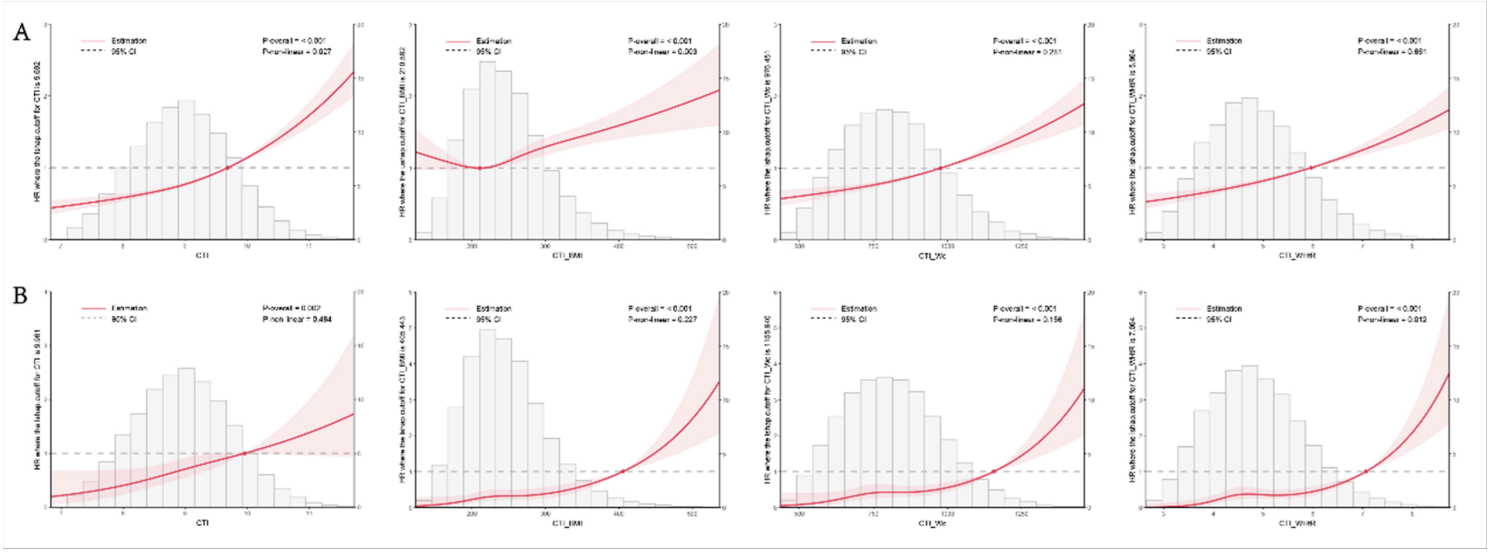


Figure 4

Associations between CTI and its obesity-related derivatives with all-cause mortality (A), and CVD-related mortality (B) evaluated by RCS after fully adjustment for the covariates.

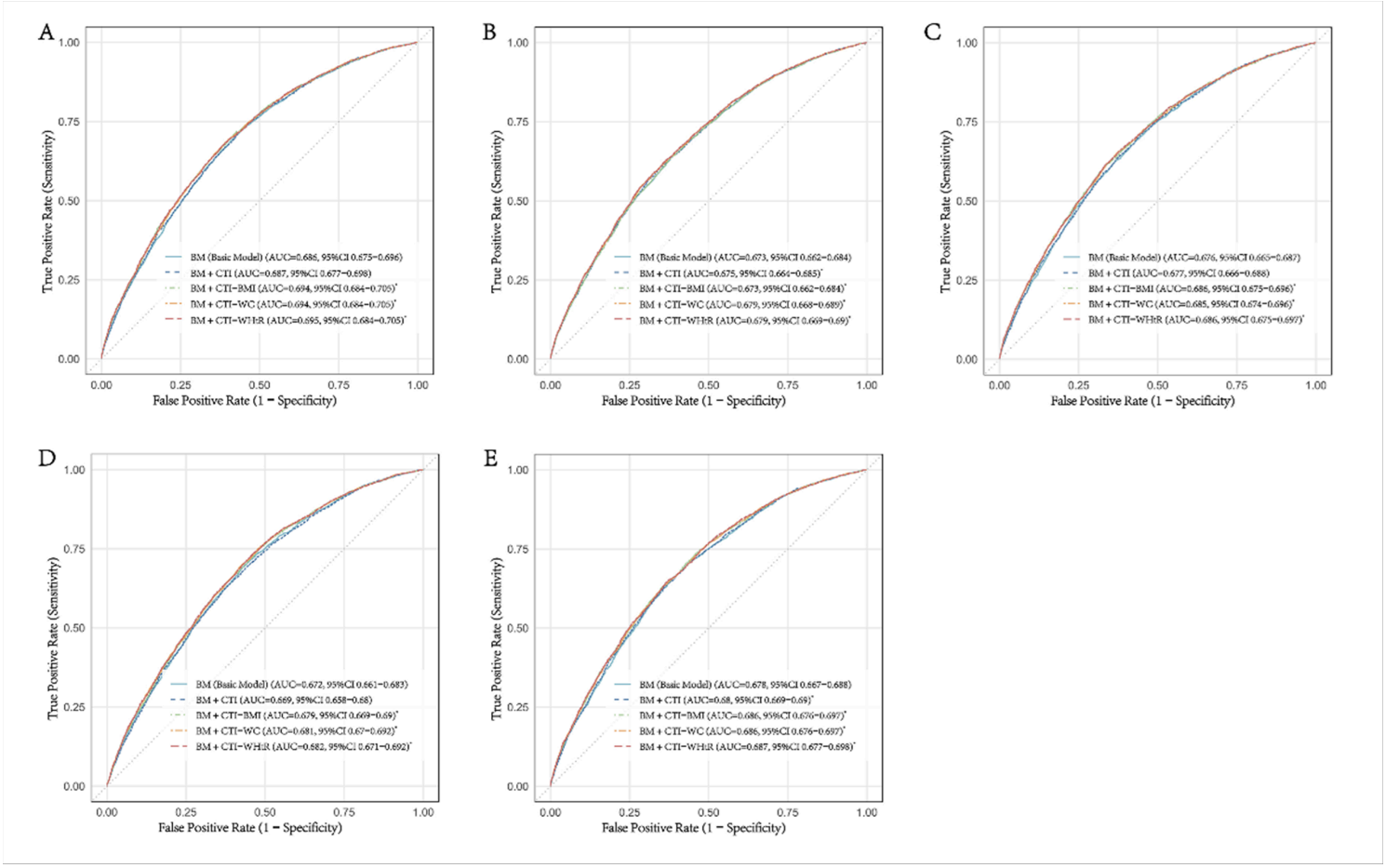


Figure 5

Receiver operating characteristic curves for total CVD events (A), stroke events (B), heart failure events (C), all-cause mortality (D), and CVD-related mortality (E) in cancer survivors. The basic model was adjusted for age, genetic sex, ethnicity, socioeconomic status, educational attainment, assessment centre, smoking status, alcohol consumption, HBA1c, HDL-C and LDL-C.
* indicates significantly improved predictive performance versus the basic model by DeLong's test ($p < 0.05$)

Supplementary Files

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