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A multimodality score strategy for assessing the risk of immune checkpoint inhibitors related cardiotoxicity

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This study aimed to find the association between four common clinical biomarkers and subsequent ICICT, developing a risk scoring strategy to assess the ICICT risk. Three terminals for ICICT were : Terminal 1, cancer therapy-related cardiomyopathies; Terminal 2, myocarditis or heart failure; and Terminal 3, myocarditis, heart failure, myocardial infarction, cerebral infarction, atrial fibrillation, or death. The thresholds were : N-terminal-pro-B-type-natriuretic-peptide ≥ 125 pg/mL, cardiac troponin T ≥ 6 ng/L, high-sensitivity C-reactive protein ≥ 3 mg/L, and coronary artery calcium score > 10 U. Each of the four abnormal biomarkers received 1 point. The links between biomarkers, score stage, and ICICT were analyzed. 375 patients with a mean follow-up of 1.91 years were included. All four biomarkers measured before immunotherapy were associated with a higher risk of developing ICICT. These scores were also associated with ICICT risk. The highest risk was the very high stage (score = 4) has 7.29, 8.83, and 7.02 folder higher risk compared to low risk group for Terminal 1–3, respectively. The cumulation of incidences also showed that the higher stages of score had an earlier onset and higher incidence of ICICT. 4 biomarkers and the scoring strategy enables clinicians to assess risk easily.

Keywords Immune checkpoint inhibitors, Cardiotoxicity, Multimodality score strategy, Cardio-oncology, Biomarkers

The increased prevalence of cancer, early detection technologies, and advanced therapies have resulted in a significant increase in cancer survivors. The cancer-related death rate has declined by 33% since 1991, with an estimated 3.8 million deaths averted[1,2]. By 2022, there were already more than 18 million cancer survivors in the United States, which is expected to reach 22.1 million by 2030, and approximately half of them have been diagnosed with cancer for more than 10 years[3]. Thus, owing to victories in fighting this disease, cancer therapy-related side effects, including cancer therapy-related cardiovascular toxicity, have attracted significant attention[2,4].

Immune checkpoint inhibitors (ICI) are monoclonal antibodies that can block negative regulators of immune activation to unleash the cancer cell killing system of CD8-positive T cells, which is a type of revolutionary anticancer therapy. In melanoma, after the use of ICI, tumor regression and long-term cancer control are possible in nearly 50% of cases, compared to less than 10% historically[5,6]. However, immune checkpoints are also important to cardiac immune homeostasis, which is a self-protection mechanism[7,8]. Therefore, over stimulation of immune system may result in immune related cardiovascular toxicity which may be severe and have a poor prognosis[2,9]. Studies have shown that ICI-related myocarditis can be fatal with the highest mortality rate of up to 50% [10,11]. Moreover, ICI-related cardiotoxicity (ICICT) is also associated with atherosclerotic cardiovascular diseases such as coronary artery disease, myocardial infarction, ischemic stroke, and arrhythmias[12–14].

These poor outcomes not only lead to a poor prognosis but also limit the use of ICI. Therefore, there is an urgent clinical need to find a way of assessing the risk of ICICT before therapy. However, there is only one study by Petricciuolo et al. that provides single-criteria discrimination of ICICT using cTnt before immunotherapy

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through a small number of sample of only 30 patients[15]. Previous studies have already suggested the promising assessment value of cardiac troponin T (cTnT), high sensitive C-reactive protein (hs-CRP), N-terminal-pro-B-type-natriuretic-peptide (NT-proBNP), and coronary artery calcification score (CAC) for the risk of cardiotoxicity[9,15–21]. For immunotherapy, most previous studies focused only on elevation after the onset of cardiotoxicity[9,18,19]. However, there is no clear evidence for their use as risk assessment factors for ICICT before initiation. Studies in other populations have already used multi-criteria methods to assess the risk of cardiovascular events, showing better potential for clinical use and efficacy[22,23]. Moreover, previous studies of ICI in cardiovascular disease typically considered a small amount of cardiotoxicity, such as cancer therapy-related cardiac dysfunction (CTRCD), myocarditis, and cardiac death; however, cardiotoxicity in populations with immunotherapy extends beyond them, and it is important to pay attention to the hazardous cardiovascular influence of ICI on the broader spectrum[2,9,12,14,23–25].

Therefore, we aimed to develop a more effective multimodality clinical risk scoring strategy (combination of cTnt, hs-crp, NT-proBNP, and CAC) that can be used to assess the broader spectrum of ICICT risk and outcome in patients using ICI and to assess the association between cTnt, hs-CRP, NT-proBNP, CAC and ICICT.

Methods

Study population

Our study population consisted of patients who had been diagnosed with carcinoma and undergone immunotherapy at the First Affiliated Hospital of Chongqing Medical University, a large general hospital located in southwest China, between January 2018 and February 2022, who met inclusion criteria and none of exclusion criteria. The detailed process is shown in Fig. 1.

The inclusion criteria were as follows: (1) Patients aged ≥ 18 years. (2) Patients who signed a consent form upon admission and agreed to the use of their medical data for medical research purposes.

The exclusion criteria were as follows: (1) Patients who had been diagnosed with heart failure, myocarditis, severe heart valve disease, myocardial infarction, atrial fibrillation, malignant arrhythmia, and cerebral infarction. (2) Patients who received anthracycline for antitumor therapy. (3) Patients with severe coronary artery disease diagnosed using coronary angiography and underwent percutaneous coronary intervention before immunotherapy. (4) Patients whose medical records were incomplete or did not provide us with sufficient necessary information. (5) Patients who were in another clinical perspective cohort while receiving ICI. (6) Patients with hematological malignancies.

The study was carried out in accordance with the Declaration of Helsinki, approved by the Ethics Committee of the Chongqing Medical University, ethics number: 2022-31. Informed consent has been obtained from all the participants in this study. Informed consent has been obtained from all the participants in this study.

Study endpoints

Three terminals were set for different ICICT as follows: Terminal 1 was cancer therapy-related cardiomyopathies, which was defined by: (1) An elevation of cTnT and NT-proBNP levels from baseline and upper limits of normal range. (2) New onset of ECG abnormalities (ST-T abnormalities, including pseudo-infarct ST segment elevation, atrial or ventricular arrhythmias, AV blocks, QRS abnormalities). (3) New onset of echocardiographic abnormalities (New structural or function abnormalities, regional wall motion abnormalities or global ventricular dysfunction without ventricular dilatation or with, generally mild, dilatation, increased wall thickness due to myocardial oedema, pericardial effusion, intracardiac thrombi, not explained by other conditions)[2,14,26–28]. Terminal 2 was defined as the new onset of myocarditis or heart failure after ICI initiation. Terminal 3 was set as a combination of a new onset of myocarditis, heart failure, myocardial infarction, cerebral infarction, atrial fibrillation, and death[2,23].

Data collection

Doctors diagnosed the patients according to the International Classification of Diseases 10th Revision (ICD-10) codes, and all other data, including medication information, were recorded in the electronic medical record system. Two eligible researchers reviewed the medical records and obtained all information about demographic and clinical characteristics, medication and anticancer therapy information, clinical diagnosis, and test results including NT-proBNP, cTnt (Tested by Automated Electrochemiluminescence Immunoassay Analyzer cobas e 411 from Roche Diagnostics GmbH, high sensitivity Cardiac Troponin T assay kit), and hs-CRP; physical examination (blood pressure and heart rate); echocardiography diagnosis; and ECG diagnosis before and after therapy. CAC Agatston scores were calculated by a professional radiologist from the computed tomography (CT) images recorded before the initiation of immunotherapy using the Philips IntelliSpace Portal software v12.1[29]. The following thresholds were selected to define elevated biomarker levels according to the previous research: NT-proBNP ≥ 125 pg/mL, cTnT ≥ 6 ng/L, hs-CRP ≥ 3 mg/L, and CAC > 10 U according to the previous studies[22,23]. The ICD-10 coded diagnosis recorded on the first page of the medical records was used to identify new-onset myocarditis, heart failure, myocardial infarction, cerebral infarction, atrial fibrillation, and death.

Statistical analysis

All the analyses were performed using R v4.1.2 (http://www.R-project.org, The R 121 Foundation). $P < 0.05$ represents statistical significance. Follow-up time was calculated from the day immunotherapy was initiated to the emergence of 3 terminals of ICICT or last follow-up date, whichever occurred first.

We used the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables to compare the baseline characteristics between different score stages. Multivariable Cox proportional hazard models were constructed to evaluate the independent association between 4 biomarkers (cTnT, NT-proBNP, hs-CRP, and CAC) and ICICT and to calculate the hazard ratio (HR) with 95% confidence interval (CI). The

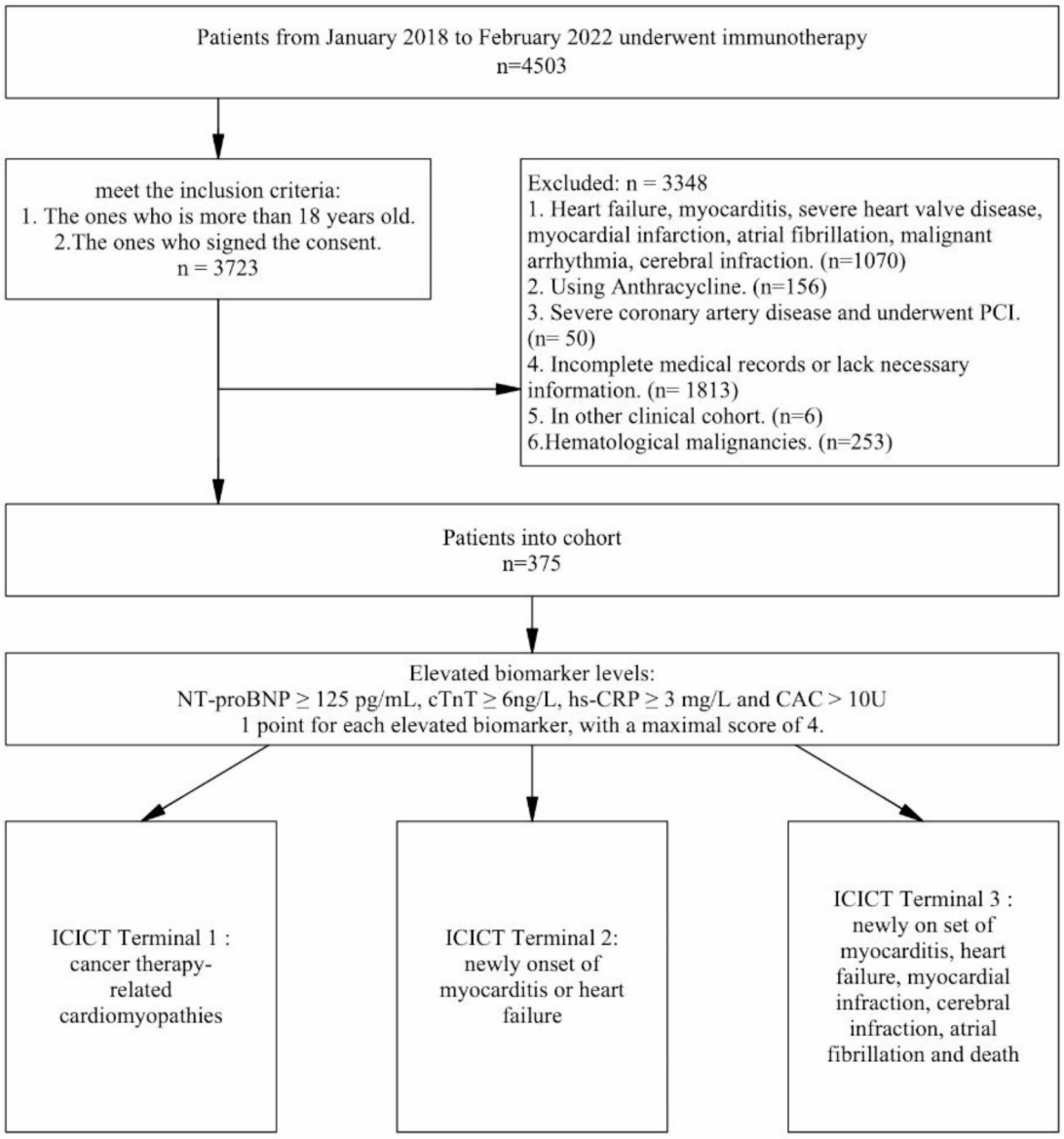

Fig. 1. Flow diagram of the study population.

biomarker score incorporated each of the four biomarkers, with one point for each abnormal biomarker and a maximum score of 4. The baseline characteristics and risk of ICICT terminals were assessed across four biomarker score stages: low (score = 0–1); medium (score = 2), high (score = 3), and very high (score = 4). Multivariable Cox proportional hazard models were constructed to evaluate the association between score stages and ICICT terminals and to calculate the HR with 95% CI. Multivariate models were constructed using serial adjustments to control for potential confounders. Model 1 included age, sex, smoking, and alcohol use; model 2 included model 1 and total cholesterol (Tc), hypertension (HTN), diabetes mellitus (DM), body mass index (BMI), ICI cycles, and ICI types; model 3 included model 2, BMI, statin use, and antihypertension agents use. To examine the reliability of the results, we also adjusted for chemotherapy, radiotherapy, targeted therapy, and the other 3 biomarkers. We also constructed a weighted score based on the four scores using the following equation: weighted work score = ($\beta1 \times$ factor $1 + \beta2 \times$ factor $2 + \ldots + \beta4 \times$ factor 4) $\times$ (4/sum of the β coefficients). The cumulative rates of the composite outcome were calculated and illustrated using the Nelson-Aalen failure estimator, and the groups were compared using the log-rank test.

Results

Basic demographic characteristics

A total of 4,503 patients who had undergone immunotherapy between January 2018 and February 2022 were identified. After filtration, 375 cases were included in our cohort (Fig. 2a). Patients included in this study had a mean age of 60.3 ± 10.1 years, and 67 (17.9%) were female. The average follow-up duration was 1.91 years. Detailed basic characteristics can be found in Supplementary Table 1.

Associations of test results with outcomes

All four tests were independently associated with the three Terminals after adjusting for traditional risk factors (Table 1). For ICICT Terminal 1, the largest hazards were observed for cTnt (HR 2.64, 95% CI: 1.28–4.3), followed by hs-CRP, CAC, and NT-proBNP. For ICICT Terminal 2, the largest hazards were observed for hs-CRP (HR 3.27, 95% CI: 1.76–6.09), followed by CAC, cTnt, and NT-proBNP. For ICICT Terminal 3, the largest hazards were observed for hs-CRP (HR 2.06, 95% CI: 1.28–3.34), followed by cTnt, NT-proBNP, and CAC. Detailed information is provided in Table 1; Fig. 2b. We re-examined the stability of the discrimination and assessment

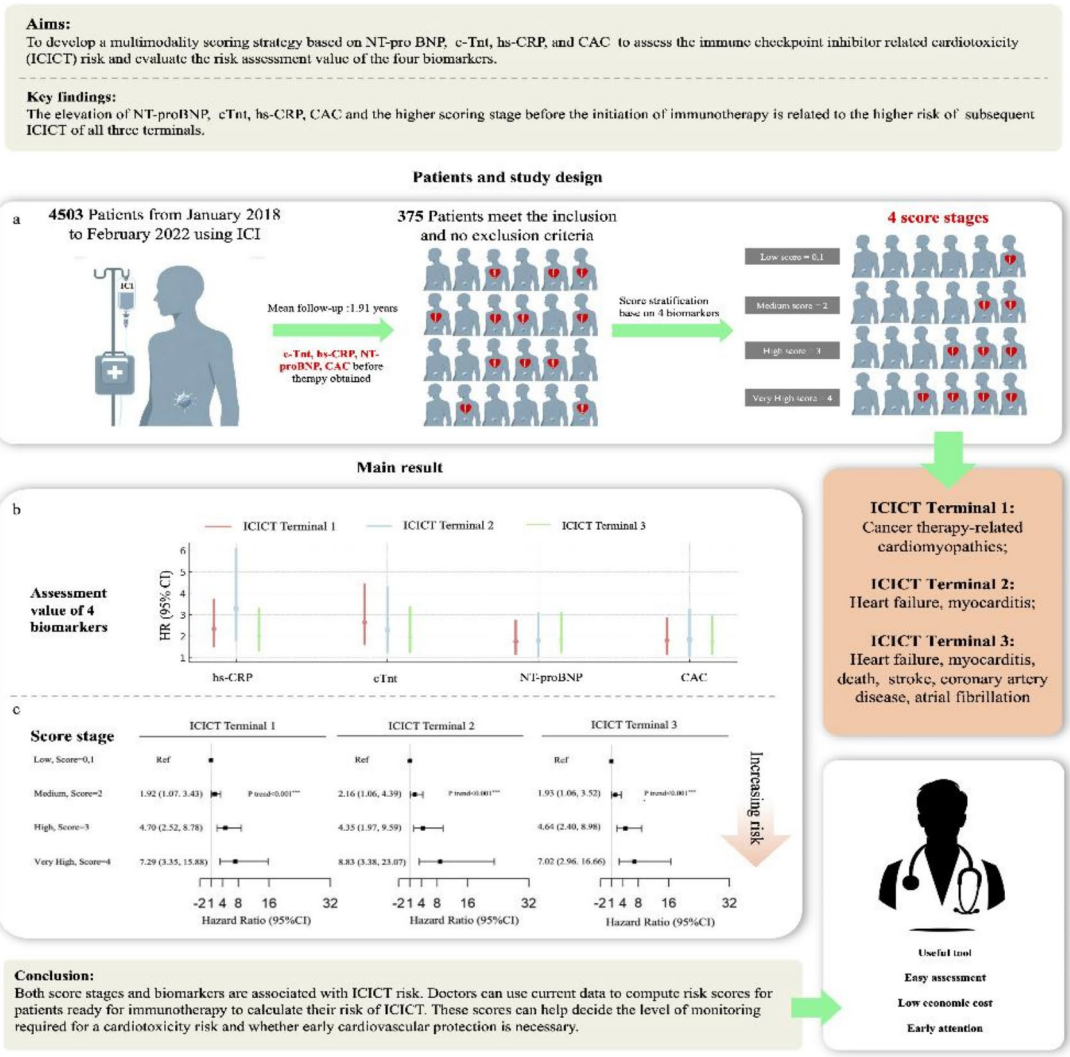

Fig. 2. Multivariable-adjusted incident ICICT risk of score stages among immunotherapy patients. (**a**) Patients and study design. (**b**) Incident risk of ICICT terminals according to the four biomarkers. (**c**) Incident risk of ICICT terminals according to the multimodal clinical risk score. Multivariable model was adjusted for age, sex, smoking, alcohol use, TC, DM, ICI cycles, ICI types (PD1, PDL1, or both), BMI, Statin use, AHAs use.

	hs-CRP	cTnt	NT-proBNP	CAC
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
ICICT terminal 1				
Model 1	2.37 (1.51, 3.72)	2.79 (1.68, 4.66)	2.56 (1.68, 3.92)	2.10 (1.38, 3.21)
Model 2	2.48 (1.56, 3.94)	2.76 (1.63, 4.66)	1.96 (1.25, 3.07)	1.99 (1.28, 3.11)
Model 3	2.35 (1.47, 3.76)	2.64 (1.56, 4.47)	1.75 (1.12, 2.75)	1.80 (1.13, 2.86)
ICICT terminal 2				
Model 1	3.03 (1.68, 5.45)	2.35 (1.28, 4.3)	2.79 (1.66, 4.69)	2.10 (1.25, 3.54)
Model 2	3.40 (1.84, 6.27)	2.38 (1.26, 4.5)	1.94 (1.11, 3.38)	2.02 (1.16, 3.51)
Model 3	3.27 (1.76, 6.09)	2.28 (1.20, 4.31)	1.79 (1.03, 3.11)	1.84 (1.04, 3.26)
ICICT terminal 3				
Model 1	1.90 (1.21, 3.00)	2.14 (1.30, 3.54)	2.89 (1.85, 4.52)	2.04 (1.31, 3.21)
Model 2	2.15 (1.34, 3.45)	2.13 (1.27, 3.57)	2.12 (1.32, 3.42)	2.01 (1.25, 3.23)
Model 3	2.06 (1.28, 3.34)	2.02 (1.21, 3.39)	1.93 (1.20, 3.12)	1.82 (1.12, 2.98)

Table 1. Multivariable-adjusted ICICT risk of four biomarker results. Model 1: Age, sex, smoking, alcohol use. Model 2: Model 1 + TC, hypertension, DM, ICI cycles, ICI types (PD1, PDL1, or both). Model 3: Model 2 + BMI, Statin use, AHAs use. ICICT Terminal 1: Cancer therapy-related cardiomyopathies; ICICT Terminal 2: heart failure, myocarditis; ICICT Terminal 3: heart failure, myocarditis, death, stroke, coronary artery disease, and atrial fibrillation. *ICICT* immune check-point inhibitors related cardiotoxicity, *ICI* immune-checkpoint inhibitors; *CAC* coronary artery calcium score, *cTnt* cardiac troponin T, *hs-CRP* high-sensitivity C-reactive protein, *NTpro-BNP* N-terminal pro b-type natriuretic peptide, *TC* total cholesterol, *DM* diabetes mellitus, *BMI* body massive index, *AHAs* antihypertension agents, *Anti-PD1* anti-programmed cell death protein 1, *Anti-PDL1* anti-programmed cell death-ligand.

values by further adjusting for the other 3 biomarkers, and each biomarker was also independently associated with the three Terminals of ICICT (Supplementary Table 4).

Multimodality risk score

Participants were assigned one point for each abnormal test result, yielding an integer score ranging from 0 to 4. Before the initiation of immunotherapy, 182 (48.53%) patients had a low score stage (score = 0–1), 118 (31.47%) patients had a medium score stage (score = 2), 57 (15.2%) patients had a high score stage (score = 3), and 18 (4.8%) patients had a very high score stage (score = 4). The detailed information is presented in Supplementary Table 1. ICICT risk was independently associated with our score stages. In multivariable-adjusted Cox analysis, a significant graded association was observed between score stages and the risk of ICICT among patients, independent of other potential confounders, with the highest risk noted among patients in the very high stage (score = 4) of all three Terminals. Compared with participants with low score, the multivariate-adjusted HR for those with a very high score was 7.29 (95% CI: 3.35–15.88) for Terminal 1, 8.83 (95% CI: 3.38–23.07) for Terminal 2, and 7.02 (95% CI: 2.96–16.66) for Terminal 3 in multivariate-adjusted model. Other details regarding the association between ICICT and score stage of 3 adjusted models are shown in the Fig. 2c; Table 2. Even after further adjustment for other cancer therapies, the association was still stable (Supplementary Table 3). The results did not change remarkably for weighted scores (Supplementary Table 2). The Kaplan-Meier estimates for the cumulation of incidences also showed that higher stages of score had a higher incidence of ICICT (Fig. 3), and higher score stages also indicated an earlier onset of ICICT. The Time-dependent Receiver Operating Characteristic Curve (ROC) analysis for 1-year risk prediction using four biomarkers and score stages is shown in Supplementary Fig. 1. The area under the ROC curve (AUC) for scores stages are 0.847, 0.854 and 0.816 for ICICT T1, T2 and T3, respectively.

Discussion

In this cohort study, we combined four promising biomarkers to stratify the cardiovascular risk among adults undergoing immunotherapy. Among included patients under immunotherapy, biomarkers of cTnt, NT-proBNP, CAC, and hs-CRP were independently associated with higher risk of ICICT, and all of them had a significant risk assessment value of ICICT (Fig. 2b; Table 2). Additionally, a simple integer score based on the levels of these biomarkers demonstrated good risk stratification of ICICT and had more significant risk gradients than the single criteria. The low-scoring stage (score = 0–1) had the lowest relative risk of ICICT. In contrast, the risk of ICICT was considerably higher in patients with high biomarker scores. Compared with the low score stage (Score = 0–1), the very high score stage (score = 4) had a 7.29-, 8.83-, and 7.02-fold higher risk ($p < 0.01$) for ICICT Terminal 1, Terminal 2, and Terminal 3, respectively, in the multivariate-adjusted model (Fig. 2c; Table 2). The Kaplan-Meier estimates for the cumulation of incidences also showed that higher scores stages had a higher incidence of ICICT (Fig. 3). A higher score stage was associated with a higher risk of poor cardiac-related outcomes among patients undergoing immunotherapy.

Previous studies didn't demonstrate a correlation between 3 (hs-CRP, NT-proBNP, CAC) of our 4 chosen biomarkers before ICI use and the risk of subsequent ICICT, and current research on the last biomarker, cTnT, is

	Score	ICICT terminal 1	ICICT terminal 2	ICICT terminal 3
		HR (95% CI)	HR (96% CI)	HR (97% CI)
Model 1	Low = 0,1	Ref	Ref	Ref
	Medium = 2	1.84 (1.03, 3.28)	1.99 (0.99, 4.01)	1.76 (0.97, 3.18)
	High = 3	5.26 (2.92, 9.47)	4.93 (2.36, 10.3)	5.04 (2.74, 9.29)
	Very high = 4	12.62 (6.09, 26.16)	16.09 (6.62, 39.11)	11.98 (5.38, 26.67)
Model 2	Low = 0,1	Ref	Ref	Ref
	Medium = 2	1.96 (1.09, 3.5)	2.15 (1.06, 4.36)	1.95 (1.07, 3.55)
	High = 3	5.19 (2.80, 9.63)	4.85 (2.21, 10.64)	5.23 (2.73, 10.01)
	Very high = 4	9.08 (4.27, 19.32)	11.14 (4.37, 28.38)	9.04 (3.89, 21.02)
Model 3	Low = 0,1	Ref	Ref	Ref
	Medium = 2	1.92 (1.07, 3.43)	2.16 (1.06, 4.39)	1.93 (1.06, 3.52)
	High = 3	4.70 (2.52, 8.78)	4.35 (1.97, 9.59)	4.64 (2.40, 8.98)
	Very High = 4	7.29 (3.35, 15.88)	8.83 (3.38, 23.07)	7.02 (2.96, 16.66)

Table 2. Multivariate-adjusted model of the association between four score stages and ICICT terminals. Model 1: Age, sex, smoking, alcohol use. Model 2: Model 1 + TC, hypertension, DM, ICI cycles, ICI types (Anti-PD1, Anti-PDL1, or both). Model 3: Model 2 + BMI, tatin use, AHAs use. ICICT Terminal 1: Cancer therapy-related cardiomyopathies; ICICT Terminal 2: heart failure, myocarditis; ICICT Terminal 3: heart failure, myocarditis, death, stroke, coronary artery disease, and atrial fibrillation. *ICICT* immune check-point inhibitors related cardiotoxicity, *ICI* immune-checkpoint inhibitors, *CAC* coronary artery calcium score, *cTnt* cardiac troponin T, *hs-CRP* high-sensitivity C-reactive protein, *NTpro-BNP* N-terminal pro b-type natriuretic peptide, *TC* total cholesterol, *DM* diabetes mellitus, *BMI* body massive index, *AHAs* antihypertension agents, *Anti-PD1* anti-programmed cell death protein 1, *Anti-PDL1* anti-programmed cell death-ligand.

also insufficient; however, similar previous studies support our research findings. CRP and hs-CRP are essential cardiovascular biomarkers used for assessing cardiovascular disease risks[20,21,30–35]. They are inflammatory indicators associated with immune-related diseases[30–33]. Previously, Iivanainen et al. and Riedl et al. found that elevated CRP or hs-CRP levels indicated poor progression-free and overall survival in patients receiving immunotherapy[34,35]. Isik et al. suggested that elevated serum CRP levels help differentiate acute kidney injury due to ICI from other causes[36]. cTnt is regarded as the most important and effective indicators of myocardial injury[2,20,21]. Kitayama et al. found that the Tnt assay could be used to assess anthracycline- and trastuzumab-induced cardiotoxicity in patients with breast cancer[37]. Lehmann et al. showed that cTnt is associated with major adverse cardiovascular events in patients with ICI myocarditis[19]. The only study examining the assessment value of cTnt for ICICT prior to immunotherapy was conducted by Petricciuolo et al., who found that baseline hs-Tnt could predict cardiovascular outcomes and cardiac progression through a sample of only 30 cases[15]. BNP/NT-proBNP is another traditional cardiac biomarker used to detect cancer therapy-related cardiovascular toxicity (CTR-CVT)[2,16,20,21,38]. Bouwer et al. found that elevated BNP/NT-proBNP levels were associated with a higher risk of trastuzumab-induced cardiotoxicity[39]. Skovgaard et al. found that BNP levels could assess cardiotoxicity and overall death in patients with cancer receiving cardiotoxic chemotherapy[40]. A meta-analysis by Michel et al. suggested the reverse idea. Their result does not suggest that NT-proBNP is a marker of cancer therapy-related cardiotoxicity[41]. This study primarily paid attention to the rise in NT-proBNP levels and left ventricular dysfunction post-cancer therapy, without other cardiotoxicity types, noting a lack of research on immunotherapy. CAC is a crucial marker for cardiovascular risk evaluation, demonstrated by earlier extensive cohort studies like the Multi-Ethnic Study of Atherosclerosis (MESA), Heinz Nixdorf Recall (HNR), and Coronary Artery Risk Development in Young Adults (CARDIA). It not only strongly predicts cardiovascular risk but also provides additional value beyond conventional risk factors, showing significant hazard ratios for cardiovascular events[23,42]. In cardio-oncology, Mascalchi et al. and Phillips et al. found a significant association between CAC and higher cardiovascular mortality and events risk in cancer patients[43,44]. Overall, our study is the first to demonstrate that the elevation of three (hs-CRP, NT-proBNP, and CAC) in our 4 chosen biomarkers before ICI initiation are strongly associated with a higher risk of ICICT later. Additionally, our study reassessed the risk assessment value of the remaining biomarker (cTnt) in a larger sample size.

Using a single indicator for risk prediction is often inadequate. Therefore, additional biomarkers are widely recommended in the clinical guidelines. The JCS 2023 guidelines for the myocarditis recommend inflammatory markers, myocardial injury markers, heart failure markers, and other tests to discriminate myocarditis[21]. Cardio-oncology guidelines also recommend NT-proBNP (or BNP), cTnt, ECG, and other criteria as risk factors for CTR-CVT[2]. However, these articles did not evaluate combinations of tests, and previous studies by de Lemos et al. and Pandey et al. have already substantiated the benefits of employing a multimodality testing approach with these biomarkers for specific individuals seeking additional risk stratification[22,23]. hs-CRP, cTnt, NT-proBNP, and CAC cover various pathological cardiac processes, such as atherosclerosis, neurohormonal activation, cardiomyocyte injury, and inflammation. These processes may involve multiple mechanisms that, when acting together, can synergistically amplify the risk of ICICT. Therefore, using these tests jointly as a multifaceted scoring strategy to assess the risk of ICICT shows promising potential.

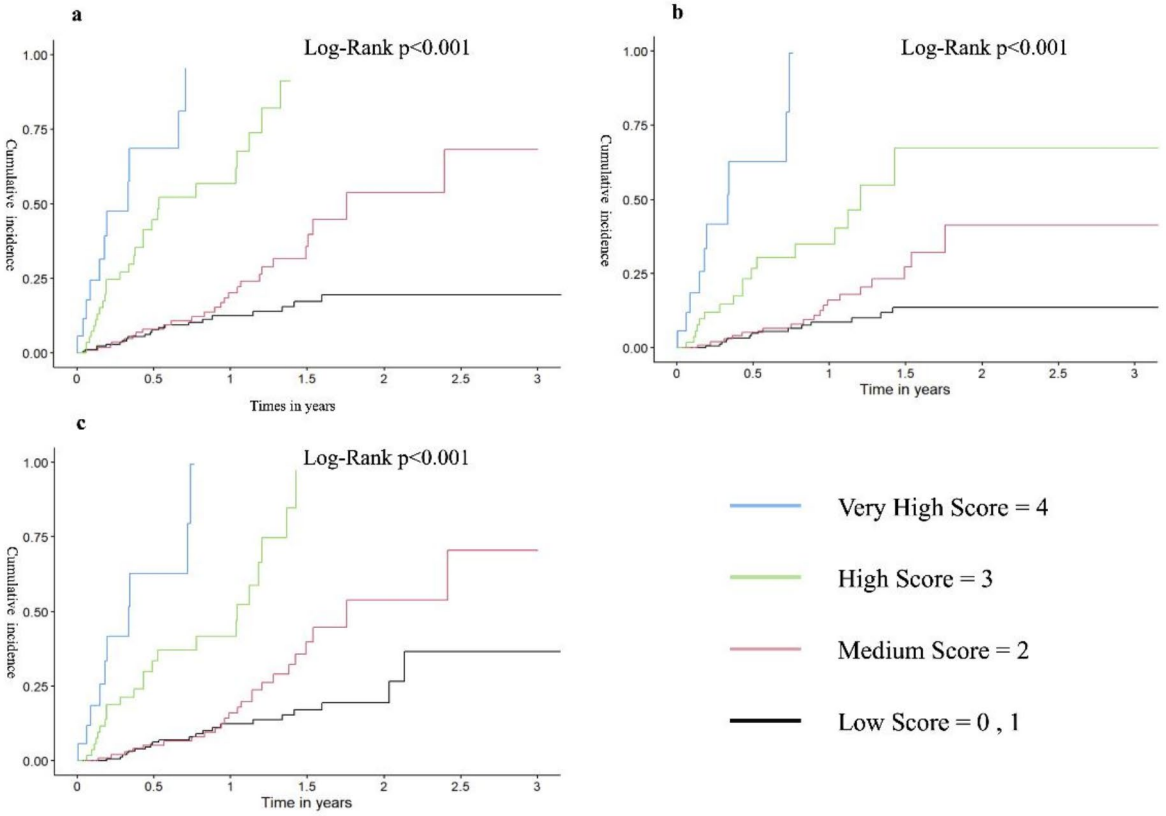

Fig. 3. Kaplan Meir estimates for the cumulation of ICICT incidence events. (**a**) ICICT Terminal 1 (cardiomyopathies); (**b**) ICICT Terminal 2 (heart failure, myocarditis); (**c**) ICICT Terminal 3 (heart failure, myocarditis, death, stroke, coronary artery disease, atrial fibrillation). *ICICT* immune check-point inhibitors related cardiotoxicity.

To the best of our knowledge, this study is the first to use cTnt, hs-CRP, NT-proBNP, and CAC before the initiation of ICI to jointly create a multifaceted scoring strategy with more significant risk gradients than single criteria. Furthermore, this study is the first to reveal that the 3 (hs-CRP, NT-proBNP, and CAC) of our 4 chosen biomarkers measured before immunotherapy are strongly associated with a higher risk of subsequent ICICT. Additionally, our study reassessed the risk assessment value of the remaining biomarker (cTnt) in a larger sample size. Importantly, previous studies of ICI in cardiovascular disease typically consider a small amount of cardiotoxicity, such as CTRCD, myocarditis, and cardiac death, while the ICICT extends beyond them, and our study paid attention to the hazardous effect of ICI on the broader spectrum of other cardiovascular complications such as myocardial infarction, arrhythmia, and stroke, providing an excess cardiovascular risk in a wider range of cardiovascular diseases among patients using ICI.

Our study found the elevation of NT-proBNP, cTnt, hs-CRP, CAC and the higher scoring stages before the initiation of immunotherapy is related to the higher risk of subsequent ICICT of all three terminals. All four biomarkers are convenient, inexpensive, and clinically feasible. They do not add any difficulty to clinical practice. Doctors can easily calculate the risk scores for patients who are about to receive immunotherapy using the existing data and assess the subsequent risk ICICT. Based on the scores and grading, they can determine whether it is necessary to pay closer attention to the patient's cardiac condition and provide early cardiovascular protection if needed.

Limitation

First, it was a retrospective cohort study and bias is inevitable. Therefore, further studies are warranted. Second, biomarkers were evaluated once before immunotherapy without considering the impact of fluctuating biomarker levels after immunotherapy on ICICT risk. However, single biomarker score assessment is a straightforward and practical method for risk stratification. Third, the scores utilized categorical rather than continuous measures, may overlooking critical information at the distribution tails. However, this categorical method simplifies the usage and is potentially more amenable to adoption. Fourth, even CAC scoring can be calculated by the previous

non-contrast, non-cardiac CT scans, and various methods, such as Agatston scoring, ordinal scoring, and even visual estimation, can effectively assess the degree of coronary artery calcification, which make it easy to access in clinical practice[29], not enough attention has been paid to CAC testing and it is not yet implemented in routine clinical work, which might influence the clinical use of our research. Therefore, more attention should be paid to CAC by clinicians as the guidelines suggests. Fifth, the established cardiovascular diseases are also the important risk factors of ICICT, which may additionally increase the risk of ICICT. Therefore, attention should be paid to this group of patients in the future research. Additionally, because our study excluded patients with established cardiovascular diseases that could lead to the outcomes, or those that are part of our outcomes, to avoid confounding factors and ensure that the cardiotoxicity is as closely related to ICI as possible, the cutoffs for the biomarkers in this study may not be applicable to a cohort that includes patients with established cardiovascular diseases.

Conclusions

Among patients who underwent immunotherapy, our study found that four biomarkers (cTnT, hs-CRP, NT-proBNP, and CAC) are associated with a higher risk of ICICT before the initiation of ICI therapy, with the elevation of three (All except cTnt) being reported for the first time. Our study first used a biomarker-based integer risk-scoring strategy with these four tests before immunotherapy to assess the risk of ICICT and paid attention to the hazardous effect of ICI on a broader spectrum of other cardiovascular complications compared to previous studies. Patients with a higher biomarker score before immunotherapy have a higher risk of ICICT in real world.

Data availability

The study's datasets are not public due to privacy and ethical reasons but can be requested from the corresponding author.

Received: 19 February 2024; Accepted: 16 October 2024
Published online: 22 October 2024

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Acknowledgements

Thanks to Dr. Kanghua Lu, Dr. Zhilan Lu, Mr. Xinwu Chen and the whole research group of professor Zhong Zuo for helping with this study. Thanks to all clinicians in The 1st affiliated hospital of CQMU for medical data recording.

Author contributions

Z.C. and R.L. led this study, conducted data collection and processing, wrote the manuscript, conducted statistical analysis, and drew tables, figures. T.R. assist data collecting and manuscript submission. W.L. and M.M. assisted data collection and processing. L.T. conducted the CT image collection and CAC scoring. C.Z., Y.Z. and D.G. edited the manuscript before submission and provided consultations. Z.Z. conceived and designed this study and revised the manuscript and provided consultations. All authors have read and agreed to the published version of the manuscript.

Funding

The study was carried out in accordance with the Declaration of Helsinki, approved by the Ethics Committee of the Chongqing Medical University, ethics number: 2022-31. ZZ is supported by Chongqing Medical Scientific Research project (Joint project of Chongqing Health Commission and Science and Technology Bureau) (No.2023ZDXM011) and CQMU Program for Youth Innovation in Future Medicine (No. W0188); DSG is supported by National Natural Science Foundation of China (No. 81701384) and Municipal Education Commission (No.KJQN202100462).

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-76829-5.

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