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ORIGINAL ARTICLE

Prediabetes is associated with increased cardiac events in patients with cancer who are prescribed anthracyclines

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Abstract

Background: Prediabetes, which is a precedent of overt diabetes, is a known risk factor for adverse cardiovascular outcomes. Its impact on adverse cardiovascular outcomes in patients with cancer who are prescribed anthracycline-containing chemotherapy (ACT) is uncertain. The objective of this study was to evaluate the association of prediabetes with cardiovascular events in patients with cancer who are prescribed ACT.

Methods: The authors identified patients with cancer who received ACT from 2000 to 2019 from Clinical Data Analysis Reporting System of Hong Kong. Patients were divided into diabetes, prediabetes, and normoglycemia groups based on their baseline glycemic profile. The Primary outcome, a *major adverse cardiovascular event* (MACE), was the composite event of hospitalization for heart failure and cardiovascular death.

Results: Among 12,649 patients at baseline, 3997 had prediabetes, and 5622 had diabetes. Over median follow-up of 8.7 years, the incidence of MACE was 211 (7.0%) in the normoglycemia group, 358 (9.0%) in the prediabetes group, and 728 (12.9%) in the diabetes group. Compared with normoglycemia, prediabetes (adjusted hazard ratio [HR], 1.20; 95% confidence interval [CI], 1.01–1.43) and diabetes (adjusted HR, 1.46; 95% CI, 1.24–1.70) were associated with an increased risk of MACE. In the prediabetes group, 475 patients (18%) progressed to overt diabetes and exhibited a greater risk of MACE (adjusted HR, 1.76; 95% CI, 1.31–2.36) compared with patients who remained prediabetic.

Conclusions: In patients with cancer who received ACT, those who had prediabetes at baseline and those who progressed to diabetes at follow-up had an increased risk of MACE. The optimization of cardiovascular risk factor management, including

The first two authors contributed equally to this article.

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prediabetes, should be considered in patients with cancer who are treated before and during ACT to reduce cardiovascular risk.

Plain Language Summary

- Patients with cancer who have preexisting diabetes have a higher risk of cardiovascular events, and prediabetes is often overlooked.
- In this study of 12,649 patients with cancer identified in the Clinical Data Analysis Reporting System of Hong Kong who were receiving treatment with anthracycline drugs, prediabetes was correlated with increased deaths from cardiovascular disease and/or hospitalizations for heart failure.
- Patients who progressed from prediabetes to diabetes within 2 years had an increased risk of combined hospitalization for heart failure and death from cardiovascular disease.
- These findings indicate the importance of paying greater attention to cardiovascular risk factors, including how prediabetes is managed, in patients who have cancer and are receiving chemotherapy with anthracyclines, emphasizing the need for surveillance, follow-up strategies, and consideration of prediabetes management in cancer care.

KEYWORDS
anthracyclines, cardio-oncology, cardiovascular mortality, heart failure, prediabetes

INTRODUCTION

Although novel cancer therapies have evolved considerably over the past decades, anthracycline-containing chemotherapy (ACT) remains the cornerstone of chemotherapeutic regimens for many solid and hemogenic malignancies.[1] Its clinical effectiveness is nonetheless limited by the off-target, dose-dependent anthracycline-induced cardiotoxicity (AIC), which increases the risk of heart failure (HF) by 30% with substantial morbidity and mortality.[2–4]

Type 2 diabetes is an established risk factor in the development of HF and mortality for patients with cancer who are prescribed ACT[5,6] and is currently cited as a moderate risk factor for AIC in the European Society of Cardiology guidelines on cardio-oncology.[7] Prediabetes, as an antecedent of diabetes, is likewise associated with adverse events in the general population[8] and in those who have underlying cardiovascular disease.[9,10] The potential added risk incurred by prediabetes in patients receiving ACT remains unexplored. The objective of this study was to elucidate the association of baseline glycemic status (both prediabetes and diabetes) with long-term prognosis in patients who are prescribed ACT.

MATERIALS AND METHODS

Study design and participants

The Clinical Data Analysis Reporting System (CDARS) is a territory-wide database developed by the Hong Kong Hospital Authority (HA) and has recorded clinical inpatient and outpatient information since January 1, 1993. The HA is a statutory body that manages all public hospitals and health care institutes, providing over 80% of inpatient services to approximately 7.5 million Hong Kong citizens (https://www3.ha.org.hk/data/HAStatistics, Accessed April 20, 2024). Patients are anonymized and assigned a unique reference key in CDARS. The University of Hong Kong Institutional Review Board and the West Cluster of the HA approved this study (UW 21–270). Informed consent was waived because all data provided by CDARS was retrospective and anonymous.

All chemotherapy-naive adult patients with a solid or hematologic malignancy who were prescribed ACT (daunorubicin, doxorubicin, epirubicin, mitoxantrone, or idarubicin) for at least one episode between January 1, 2000, and December 31, 2019, were enrolled. The index date was defined as the first date of anthracycline use. Patients with an extremely short life expectancy (<14 days) were excluded. Cumulative anthracycline doses were calculated as the total dose converted to the doxorubicin equivalent divided by body surface area (m^2, 0.0061 × height [m] + 0.0124 × weight [kg] − 0.0099), using a conversion factor of 0.6, 0.8, 10.5, and 5.0 for daunorubicin, epirubicin, mitoxantrone, and idarubicin, respectively.[7]

Data collection

Baseline characteristics, including age, sex, diagnoses (etiology and metastasis), comorbidities (cerebrovascular disease, chronic HF, atrial fibrillation [AF], hypertension [HTN], chronic kidney disease,

and coronary artery disease [CAD]), drug prescriptions (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker [ACEI/ARB], statin, antidiabetes drug [insulin, metformin, sulfonylurea, meglitinide, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists], chemotherapy regimens), laboratory investigations, hospitalization details, and outpatient visits were prospectively collected by CDARS. The International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) were used to code diagnoses in CDARS (summarized in Table S1) with a high degree of coding accuracy, as previously reported.[11,12]

Definition of diabetes and prediabetes

Glycemic status was determined at the index admission using available variables (fasting blood glucose [FBG] or hemoglobin A1c [HbA1c]) from the previous 2 years. Patients who had confirmed type 2 diabetes mellitus (ICD-9 code 250.X, ICD-10 code E11) or who were prescribed antidiabetic medication in the year before their index admission were assigned to the diabetes group. Patients with no FBG or HbA1c results available in the 2 years before the index admission date (defined as the *unscreened group*) and those diagnosed with type 1 diabetes were excluded. Patients who had no diagnosis of diabetes or who had never been prescribed ant-diabetic medications were subsequently assigned depending on their blood glucose status (Figure 1), as reported previously with reference to the diagnostic criteria the Clalit Research Institute diabetes algorithm described by Karpati et al.,[13,14] adapted from American Diabetes Association parameters.[15]

Excluding patients who had *major cardiovascular events* (MACEs) within 2 years, patients in the prediabetes group were further classified and analyzed based on their glycemic status 2 years after the index date, as follows (see Figure S1): (1) *progression to diabetes* (newly diagnosed diabetes or prescription of antidiabetic drugs for ≥90 days consecutively; or two FBG tests within a period of 6 months, both ≥126 mg/dL; or two HbA1c tests within a period of 1 year, both ≥6.5%; or one FBG test ≥126 mg/dL and one HbA1c test ≥6.5% within a period of 1 year); (2) *persistent prediabetes* (no diagnosis of diabetes; and no prescription of antidiabetic medication; and no record of FBG test ≥126 mg/dL or HbA1c test ≥6.5% in the 2 years after the index date; and two FBG tests, both 100–125 mg/dL within a period of 6 months; or two HbA1c tests, both 5.7%–6.4% within 1 year; or one FBG test 100–125 mg/dL and one HbA1c test 5.7%–6.4% within 1 year; and (3) *reversion to normoglycemia* (no diagnosis of diabetes and no history of antidiabetic medications; and no record of FBG test ≥100 mg/dL or HbA1c test ≥5.7% in the 2 years after the index date).

Outcomes

The primary end point, MACE, was defined as the composite of cardiovascular mortality and HF hospitalization, whichever happened first. The secondary outcomes included all-cause mortality,

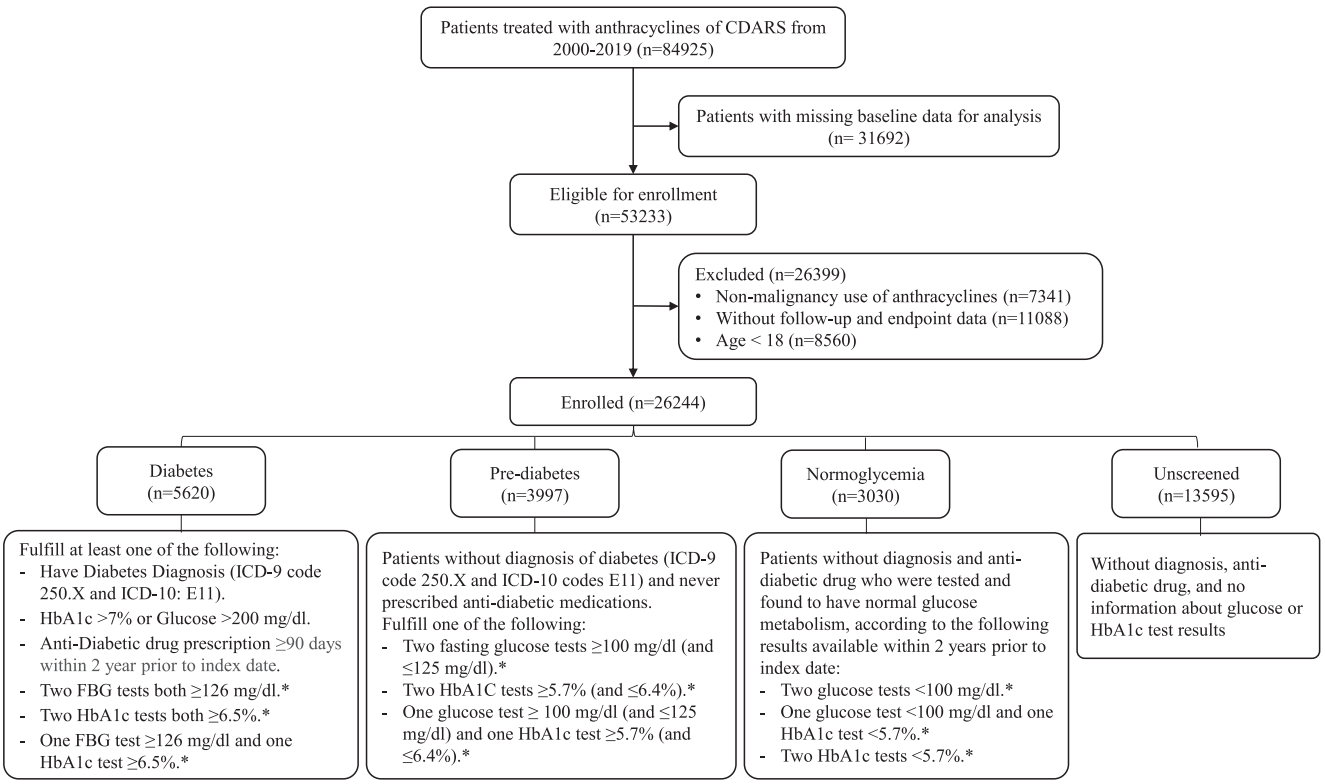

FIGURE 1 Study flowchart and criteria. *Within a period of 1 year. CDARS indicates Clinical Data Analysis Reporting System of Hong Kong; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision.

cardiovascular mortality, and HF hospitalization. Linked mortality records were retrieved and identified by the assigned ICD-10 code (cardiovascular cause, codes I00–I99). Episodes of HF hospitalization were indicated by the relevant hospital discharge ICD-10 codes. Patients were followed up from the day after the index date until the occurrence of outcomes, death, or the last date of collection (August 1, 2022), whichever came first.

Statistical analysis

Patient characteristics are presented as medians and interquartile ranges or as percentages, as appropriate. Data normality was evaluated using the Kolmogorov–Smirnov test. We used multiple imputation by chained equations based on a random forest algorithm using the *mice* package in R (R Foundation for Statistical Computing) to replace missing data for the six variables (for details, see Table S2). Fine–Gray regression and Cox proportional hazards were performed to examine the association of glycemic status with MACE. Associations were adjusted for age, sex, body mass index, white blood cell count, hemoglobin, platelets, albumin, estimated glomerular filtration rate, HTN, AF, CAD, tumor type, metastasis, medication (including ACEI/ARB, statin, anthracycline, HER2 inhibitor, and other chemotherapy), and the cumulative anthracycline doses. The hazard ratio (HR) and 95% confidence interval (CI) were estimated for MACE and for secondary end points. The incidence of end point is represented as the number of events per 100 person-years of follow-up. The cumulative survival rate was calculated using the Kaplan–Meier method, and the log-rank test used to compare groups. Stratification analyses and likelihood ratio tests were conducted to examine whether the effect of glycemic profile differed across subgroups.

In the prediabetes group, the subsequent risk of MACE was further evaluated based on changes in glycemic status 2 years after the index date. A multivariable Cox proportional-hazards model with the Fine and Gray model (with all-cause mortality defined as the competing event) were used to evaluate the risk of an end point associated with progression (to diabetes) or reversion (to normoglycemia) of prediabetes, with persistent prediabetes defined as the referent.

Sensitivity analyses were conducted in the following populations: (1) with further adjustment for blood pressure; (2) excluded patients who had an episode of HF hospitalization or death within 30 days, 90 days, and 1 year of the index date; and (3) for loss to follow-up by censoring at the last clinic visit date.

All statistical analyses were conducted using SPSS (version 25; IBM Corporation.) and R Statistical Software (version 4.1.0), with a two-sided p value $< .05$ considered statistically significant.

RESULTS

Participant characteristics

We identified a total of 26,244 patients who were prescribed ACT, of whom 13,595 (median age, 56 years; 45.3% male) had no baseline glycemic status available and were considered unscreened patients (see Table S3). Among the remaining patients, 3030 (24.0%) were classified as normoglycemic at baseline, 3997 (31.6%) were classified as prediabetic, and 5622 (44.4%) were classified as diabetic for further analysis. The baseline characteristics of the patient population (median age, 62 years; 55.5% male) are listed in Table 1. Patients who had diabetes were older, more frequently were male, had a higher prevalence of comorbidities (HF, HTN, and CAD), and had a lower median estimated glomerular filtration rate. The median cumulative dose of anthracycline in the study population was 186.70 mg/m^2.

Primary outcome

During a median follow-up of 8.7 years, we identified a total of 1297 patients who had MACE ($n = 512$ cardiovascular mortality events and $n = 950$ HF hospitalizations). The incidence of MACE was 211 (7.0%) in the normoglycemia group, 358 (9.0%) in the prediabetes group, and 728 (12.9%) in the diabetes group (p between groups $< .001$). The crude incidence rate of MACE per 100 person-years of follow-up was 1.03 (95% CI, 0.90–1.18) in the normoglycemia group, 1.57 (95% CI, 1.41–1.74) the in prediabetes group, and 2.56 (95% CI, 2.38–2.75) in the diabetes group.

In the Fine–Gray competing risk regression model, the subdistribution hazard of MACE, cardiovascular deaths, and HF hospitalizations were generally consistent with the above analysis. The prediabetes group (adjusted stress hyperglycemia ratio, 1.16; 95% CI, 0.98–1.38) and the diabetes group (adjusted stress hyperglycemia ratio, 1.40; 95% CI, 1.19–1.64) showed significant increase in the risk of MACE compared with the normal normoglycemia patients (p for trend $< .001$; Table 2).

Compared with the normoglycemia group, the unadjusted HR for MACE was 1.48 (95% CI, 1.24–1.75) in the prediabetes group and 2.34 (95% CI, 2.01–2.73) in the diabetes group (p for trend $< .001$; Table 3). After adjustment for confounding factors, the presence of prediabetes (adjusted HR, 1.20; 95% CI, 1.01–1.43) and diabetes (adjusted HR, 1.46; 95% CI, 1.24–1.70) retained the association with a higher risk of MACE compared with the normoglycemia group (p for trend $< .001$; Figure 2A).

The prevalence of MACE in both the prediabetes group and the diabetes group was consistent across most of the prespecified subgroups examined (with p values for interaction $> .05$, as detailed in Table 4). It is worth noting that patients who did not receive baseline ACEI/ARB therapy and those who had a higher cumulative dose of ACT (greater than or equal to the median dose) had more unfavorable outcomes compared with their counterparts (with p values for interaction of .045 and .023, respectively).

Secondary outcomes

In the normoglycemia, prediabetes, and diabetes groups, the crude incidence rate for all-cause mortality was 7.72, 10.0, and 11.8 per

TABLE 1 Baseline characteristics.

	No. (%) or median [IQR]			
	All patients	**Normoglycemia**	**Prediabetes**	**Diabetes mellitus**
Participants	12,649	3030	3997	5622
Male	7025 (55.5)	1525 (50.3)	2191 (54.8)	3309 (58.9)
Age, years	62 [52–74]	57 [47–70]	61 [50–73]	67 [57–76]
Body mass index, kg/m^2	24.57 (4.18)	24.08 (4.09)	24.64 (4.14)	24.75 (4.22)
WBC, 10^9/L	7.49 [5.80–9.90]	7.00 [5.50–9.10]	7.50 [5.90–10.10]	7.70 [5.90–10.20]
Hemoglobin, g/dL	12.60 [11.00–13.80]	12.70 [11.20–13.80]	12.60 [10.90–13.80]	12.50 [10.90–13.70]
Platelets, 10^9/L	226.00 [174.00–288.00]	235.00 [183.25–296.00]	229.00 [173.00–290.00]	220.00 [170.00–280.00]
Albumin, g/L	39.00 [35.00–42.00]	39.00 [36.00–42.00]	39.00 [35.00–42.00]	38.50 [35.00–42.00]
AST, U/L	24.00 [18.00–35.00]	23.10 [18.00–33.00]	24.00 [18.00–34.00]	24.00 [19.00–37.90]
eGFR, mL/(minute × 1.73 m^2)	81.03 [64.89–97.74]	85.68 [69.84–102.47]	83.03 [67.82–99.25]	76.74 [59.91–93.69]
Baseline comorbidity				
Heart failure	291 (2.3)	40 (1.3)	88 (2.2)	163 (2.9)
Atrial fibrillation	395 (3.1)	74 (2.4)	139 (3.5)	182 (3.2)
Hypertension	1843 (14.6)	249 (8.2)	497 (12.4)	1097 (19.5)
Coronary artery disease	288 (2.3)	60 (2.0)	91 (2.3)	137 (2.4)
Etiology				
Hematologic diseases	4194 (33.2)	980 (32.3)	1406 (35.2)	1808 (32.2)
Malignant neoplasm of bladder	3083 (24.4)	579 (19.1)	874 (21.9)	1630 (29.0)
Malignant neoplasm of breast	1302 (10.3)	456 (15.0)	422 (10.6)	424 (7.5)
Nonspecific neoplasm	4070 (32.2)	1015 (33.5)	1295 (32.4)	1760 (31.3)
Metastasis	2541 (20.1)	635 (21.0)	859 (21.5)	1047 (18.6)
Statin	2218 (17.5)	276 (9.1)	531 (13.3)	1411 (25.1)
ACEI/ARB	1943 (15.4)	198 (6.5)	409 (10.2)	1336 (23.8)
Estrogen receptor	766 (6.1)	201 (6.6)	241 (6.0)	324 (5.8)
HER2 inhibitors (%)	219 (1.7)	56 (1.8)	69 (1.7)	94 (1.7)
Other chemotherapy regimen	5583 (44.1)	1483 (48.9)	1838 (46.0)	2262 (40.2)
Steroids during treatment	8630 (68.2)	2118 (69.9)	2823 (70.6)	3689 (65.6)
Anthracycline type				
Daunorubicin	895 (7.1)	163 (5.4)	358 (9.0)	374 (6.7)
Doxorubicin	3497 (27.6)	971 (32.0)	1170 (29.3)	1356 (24.1)
Epirubicin	2338 (18.5)	626 (20.7)	725 (18.1)	987 (17.6)
Mitoxantrone	5077 (40.1)	1002 (33.1)	1479 (37.0)	2596 (46.2)
Idarubicin	842 (6.7)	268 (8.8)	265 (6.6)	309 (5.5)
Total dosing, mg	241.81 [80.00–288.40]	237.98 [88.00–300.00]	234.40 [88.00–285.06]	240.00 [85.00–284.87]
Cumulative dosing, mg/m^2	186.70 [99.48–392.00]	195.98 [103.07–400.38]	182.39 [105.47–384.24]	174.02 [93.82–368.94]

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; AST, aspartate aminotransferase; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; eGFR, estimated glomerular filtration rate; WBC: White blood cell count.

[a]Values are presented as no. (%) or median [IQR].

TABLE 2 Risks of end point events (major adverse cardiovascular event—cardiovascular mortality and hospitalization for heart failure) with all-cause mortality as a competing event: Fine and Gray regression model.

	Normoglycemic, *n* = 3030	Prediabetes. *n* = 3997	Diabetes, *n* = 5622	*p* for trend
MACE				
Subdistribution HR (95% CI)	1.00 (Reference)	1.34 (1.13–1.58)	2.01 (1.73–2.34)	< .001
Adjusted HR (95% CI)[a]	1.00 (Reference)	1.16 (0.98–1.38)	1.40 (1.19–1.64)	< .001
Cardiovascular mortality				
Subdistribution HR (95% CI)	1.00 (Reference)	1.36 (1.05–1.76)	1.69 (1.33–2.14)	< .001
Adjusted HR (95% CI)[a]	1.00 (Reference)	1.16 (0.89–1.50)	1.22 (0.93–1.64)	.070
Hospitalization for heart failure				
Subdistribution HR (95% CI)	1.00 (Reference)	1.37 (1.12–1.68)	2.22 (1.84–2.66)	< .001
Adjusted HR (95% CI)[a]	1.00 (Reference)	1.19 (0.96–1.46)	1.56 (1.29–1.88)	< .001

Abbreviations: CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular composite events.

[a]Model adjusted for: age, sex, body mass index, white blood cell count, hemoglobin, platelet count, serum albumin, estimated glomerular filtration rate, hypertension, atrial fibrillation, coronary artery disease, tumor type, metastasis, renin-angiotensin system inhibitors use, statin use, cumulative dosing, and other classes of chemotherapy drugs.

TABLE 3 Incidence rates and risks of end point events (major adverse cardiovascular event, all-cause mortality, cardiovascular mortality, and hospitalization for heart failure) per 100 person-years of follow-up.

	Normoglycemic, *n* = 3030	Prediabetes, *n* = 3997	Diabetes, *n* = 5622	*p* for trend
Major adverse cardiovascular event, No. (%)	211 (7.0)	358 (9.0)	728 (12.9)	
Crude incidence per 100 person-years [95% CI]	1.03 [0.90–1.18]	1.57 [1.41–1.74]	2.56 [2.38–2.75]	
Unadjusted HR [95% CI]	1.00 [Reference]	1.48 [1.24–1.75]	2.34 [2.01–2.73]	< .001
Adjusted HR [95% CI][a]	1.00 [Reference]	1.20 [1.01–1.43]	1.46 [1.24–1.70]	< .001
All-cause mortality, No. (%)	1590 (52.4)	2324 (58.1)	3514 (62.5)	
Crude incidence per 100 person-years [95% CI]	7.72 [7.34–8.10]	10.0 [9.61–10.4]	11.8 [11.4–12.2]	
Unadjusted HR [95% CI]	1.00 [Reference]	1.23 [1.15–1.31]	1.38 [1.30–1.46]	< .001
Adjusted HR [95% CI][a]	1.00 [Reference]	1.11 [1.04–1.18]	1.14 [1.07–1.21]	< .001
Cardiovascular mortality, No. (%)	92 (3.0)	156 (3.9)	266 (4.7)	
Crude incidence per 100 person-years [95% CI]	0.43 [0.35–0.53]	0.66 [0.56–0.78]	0.89 [0.78–1.00]	
Unadjusted HR [95% CI]	1.00 [Reference]	1.53 [1.18–1.99]	2.04 [1.60–2.59]	< .001
Adjusted HR [95% CI][a]	1.00 [Reference]	1.16 [0.95–1.56]	1.33 [1.04–1.69]	.023
Hospitalization for heart failure, No. (%)	150 (5.0)	253 (6.3)	553 (9.8)	
Crude incidence per 100 person-years [95% CI]	0.71 [0.60–0.83]	1.11 [0.98–1.25]	1.94 [1.79–2.11]	
Unadjusted HR [95% CI]	1.00 [Reference]	1.52 [1.24–1.87]	2.59 [2.15–3.11]	< .001
Adjusted HR [95% CI][a]	1.00 [Reference]	1.24 [1.01–1.52]	1.61 [1.33–1.94]	< .001

Note: Crude incidence rates of primary end point events per 100 person-years of follow-up in each group and the HR for the risk of primary end point events according to glycemic status compared with normoglycemic individuals.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Model adjusted for: age, sex, body mass index, white blood cell count, hemoglobin, platelet count, serum albumin, estimated glomerular filtration rate, hypertension, atrial fibrillation, coronary artery disease, tumor type, metastasis, renin-angiotensin system inhibitors use, statin use, cumulative dosing, and other classes of chemotherapy drugs.

100 person-years, respectively; the crude incidence rate for cardiovascular mortality was 0.43, 0.66, and 0.89 per 100 person-years, respectively; and the crude incidence rate for HF hospitalization was 0.71, 1.11, and 1.94 per 100 person-years, respectively. The unadjusted HR for all three secondary outcomes in patients who had prediabetes and diabetes was higher compared with that for patients

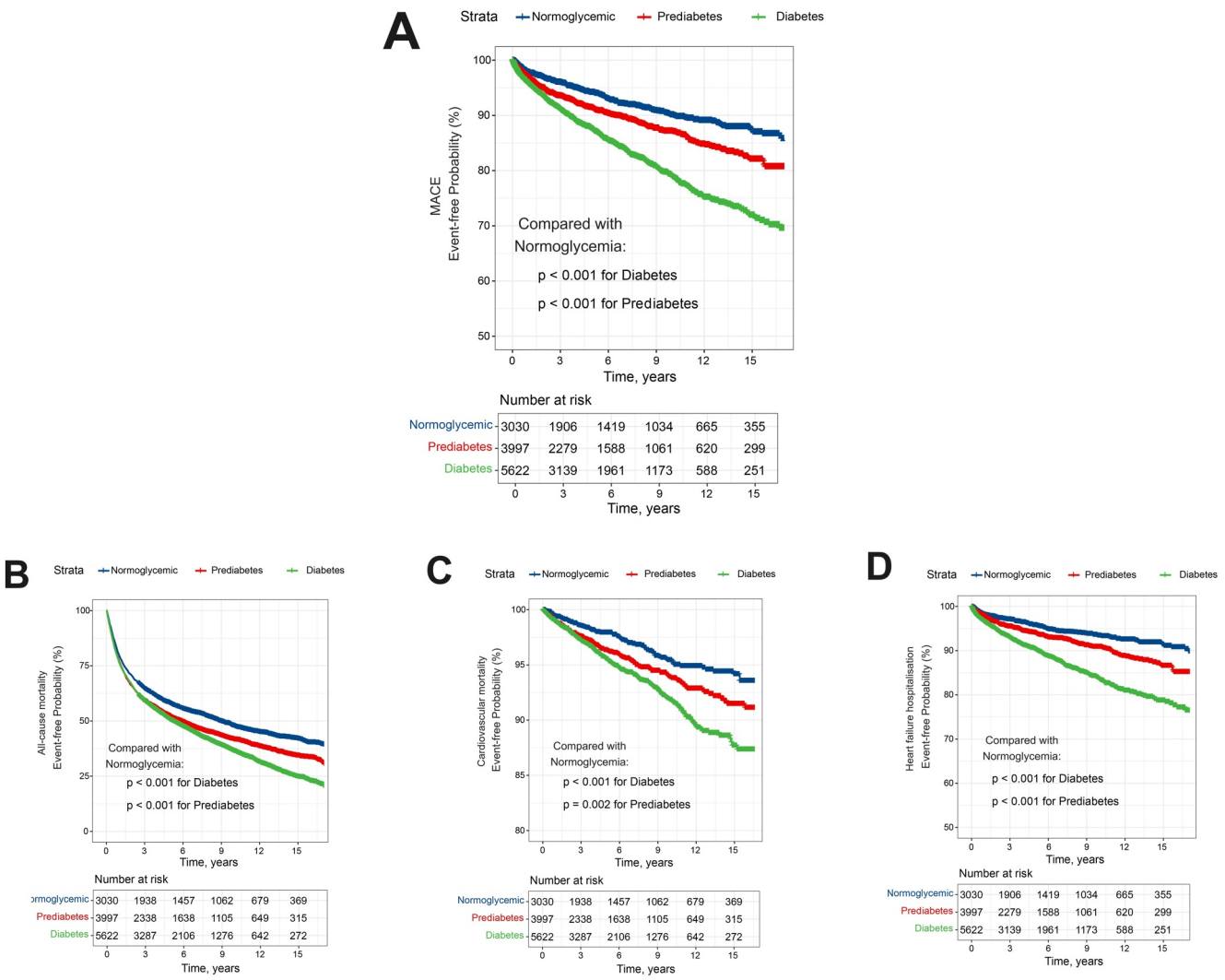

FIGURE 2 Kaplan–Meier analysis of glycemic status for the end point events in patients with cancer who were treated with anthracyclines. (A) MACE—cardiovascular mortality and heart failure hospitalization; (B) all-cause mortality; (C) cardiovascular mortality; (D) heart failure hospitalization. MACE indicates major adverse cardiovascular events.

in the normoglycemia group (all p for trend < .001) and remained consistent after adjustment for potential confounders (all p for trend < .05; Table 3 and Figure 2B–D).

Risk assessment in patients with prediabetes

Compared with the patients who remained normoglycemic (crude incidence of MACE) throughout the 2-year follow-up, patients who remained prediabetic had a 25% higher risk of MACE (adjusted HR, 1.25; 95% CI, 1.04–1.51; p = .03), whereas those who remained diabetic had a 63% higher risk of MACE (adjusted HR, 1.63; 95% CI, 1.35–1.97; p = .021; see Table S4). Among the patients who had prediabetes at baseline and were without MACE during the first 2 years of follow-up, 2637 had their glycemic status reassessed 2 years after the index date, of whom 433 (16.4%) had reversed to normoglycemia, 1729 (65.6%) had remained prediabetic, and 475 (18.0%) had progressed to diabetes. The incidence of MACE was 33 (7.6%) in the patients who reverted to normoglycemia, 228 (13.2%) in those who had persistent prediabetes, and 97 (20.4%) in those who progressed to diabetes (see Figure S1). Patients who progressed to diabetes had a higher risk of MACE than those who remained prediabetic (adjusted HR, 1.76; 95% CI, 1.31–2.36; p < .001). No difference in the occurrence of MACE was observed between patients who reverted to normoglycemia and those who remained prediabetic (see Table S5).

Sensitivity analyses

After further adjustment for blood pressure, the analysis demonstrated that patients with prediabetes and diabetes were at higher risk of study end points than those with normoglycemia (all p for trend < .05; see Table S6). After the exclusion of patients who had an episode of HF hospitalization or death within 30 days, 90 days, and 1 year of the index date, the results demonstrated findings consistent

TABLE 4 Subgroups analysis of adjusted hazard ratios for the risks of primary end point events (hospitalization for heart failure and cardiovascular mortality).

		HR (95% CI)			
Subgroup	**No.**	**Normoglycemic**	**Prediabetes**	**Diabetes**	***p* for interaction**
Age, years					.604
<65	6695	1.00 (Reference)	1.19 (0.87–1.61)	1.57 (1.17–2.11)	
≥65	5954	1.00 (Reference)	1.27 (1.03–1.56)	1.45 (1.20–1.75)	
Sex					.424
Male	7025	1.00 (Reference)	1.16 (0.92–1.45)	1.48 (1.21–1.81)	
Female	5624	1.00 (Reference)	1.25 (0.96–1.63)	1.43 (1.11–1.83)	
Baseline HTN					.836
Yes	1843	1.00 (Reference)	1.23 (0.86–1.76)	1.51 (1.09–2.10)	
No	10,806	1.00 (Reference)	1.21 (0.99–1.47)	1.43 (1.19–1.71)	
Baseline HF					.436
Yes	291	1.00 (Reference)	1.23 (0.72–2.11)	1.36 (0.82–2.23)	
No	12,358	1.00 (Reference)	1.16 (0.97–1.39)	1.43 (1.21–1.69)	
Baseline CAD					.912
Yes	288	1.00 (Reference)	1.08 (0.55–2.13)	1.11 (0.56–2.21)	
No	12,361	1.00 [Reference]	1.21 (1.02–1.45)	1.46 (1.24–1.72)	
Baseline AF					.114
Yes	395	1.00 (Reference)	1.88 (1.12–3.14)	1.55 (0.94–2.56)	
No	12,254	1.00 (Reference)	1.14 (0.95–1.36)	1.43 (1.21–1.69)	
Baseline CKD					.628
eGFR <60, mL/(minute × 1.73 m^2)	2470	1.00 (Reference)	1.20 (0.89–1.60)	1.31 (1.01–1.69)	
eGFR ≥60, mL/(minute × 1.73 m^2)	10,179	1.00 (Reference)	1.21 (0.98–1.50)	1.53 (1.25–1.86)	
Metastasis					.778
Yes	2541	1.00 (Reference)	1.14 (0.71–1.82)	1.46 (0.89–2.40)	
No	10,108	1.00 (Reference)	1.21 (1.01–1.45)	1.50 (1.25–1.78)	
Cumulative dosing					.023
≥Median	6324	1.00 (Reference)	1.23 (0.97–1.58)	1.34 (1.06–1.70)	
<Median	6325	1.00 (Reference)	1.15 (0.91–1.47)	1.13 (0.89–1.44)	
ACEI/ARB use					.045
Yes	1943	1.00 (Reference)	0.93 (0.65–1.32)	0.98 (0.712–1.34)	
No	10,706	1.00 (Reference)	1.24 (1.02–1.51)	1.51 (1.257–1.81)	
Statin use					.098
Yes	2218	1.00 (Reference)	1.06 (0.74–1.53)	1.11 (0.80–1.55)	
No	10,431	1.00 (Reference)	1.21 (0.99–1.47)	1.48 (1.22–1.76)	
Other chemotherapy					.911
Yes	5583	1.00 (Reference)	1.22 (0.87–1.72)	1.50 (1.08–2.08)	
No	7066	1.00 (Reference)	1.21 (0.99–1.48)	1.47 (1.23–1.76)	

TABLE 4 (Continued)

Subgroup	No.	HR (95% CI) Normoglycemic	Prediabetes	Diabetes	*p* for interaction
Obesity					.364
Yes	1301	1.00 (Reference)	0.84 (0.49–1.44)	1.18 (0.73–1.93)	
No	11,348	1.00 (Reference)	1.26 (1.051.51)	1.48 (1.25–1.75)	

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio.

[a]Analyses were adjusted for age, sex, body mass index, white blood cell count, hemoglobin, platelet count, serum albumin, estimated glomerular filtration rate, hypertension, atrial fibrillation, coronary artery disease, tumor type, metastasis, renin-angiotensin system inhibitors use, statin use, cumulative dosing, and other classes of chemotherapy drugs when they were not the strata variables.

with the primary analyses (all p for trend < .05; see Table S7). Among 12,649 patients, 1809 (14.3%) had no clinical activity recorded after the index visit. By censoring at the last clinic visit date, the analysis revealed that prediabetes also retained the association with a higher risk of study end points (all p for trend < .05; see Table S8).

DISCUSSION

In this territory-wide cohort study of patients with cancer who were prescribed ACT, our principal findings are as follows: (1) The incidence of MACE, comprising cardiovascular mortality and HF hospitalization, was 1.03, 1.57, and 2.56 per 100 person-years in the normoglycemia group, prediabetes group, and diabetes group, respectively. (2) After controlling for other risk factors for AIC, prediabetes was linked to a higher risk of MACE compared with normoglycemia. Furthermore, the association between MACE and prediabetic and diabetic patients was generally consistent across most subgroups. (3) Temporal changes to glycemic status in the prediabetes group further indicated that patients who progressed to diabetes had a 75% increased risk of MACE compared with those who remained prediabetic.

Cancer and diabetes are common conditions that often coexist.[16] Diabetes was the most common comorbidity, reported in up to 16% of patients with cancer.[17] In a recent study that included 3512 patients with cancer, the prevalence of diabetes was 12.2% at the time of diagnosis and 25% 1 year later.[18] In a pooled analysis of population-based cohorts, cancer survivors were 1.4 times more likely to develop diabetes than individuals without cancer.[19] Our results not only confirm that a large proportion of patients with cancer who received ACT had concomitant diabetes but also illustrate the importance of diabetes in these patients, with higher rates of complications, risk of hospitalization, and mortality versus those without diabetes.[6,7] Our study further extends this association to patients who are prescribed ACT, a population particularly prone to cardiovascular events, by demonstrating a 46% increased risk of MACE among diabetic patients compared with those who were normoglycemic.

Prediabetes, also termed *intermediate hyperglycemia*, is a high-risk metabolic state characterized by glycemic variables above normal and within the threshold for diabetes.[20–22] With its high prevalence (34.4% in the United States[22] and 15.5% in China[23]), prediabetes has become a cardinal risk factor for cardiovascular complications. The high prevalence of prediabetes observed in our study, in line with previous findings, further underlines the importance of prediabetes in patients with cancer who receive ACT. Beyond its ubiquity, a meta-analysis demonstrated that prediabetes was associated with a 13% higher risk for all-cause mortality and a 15% higher risk of composite cardiovascular disease.[24] Although a prediabetes state is a risk factor that may be mitigated by preventive interventions,[25] its role in patients who are receiving ACT has not been evaluated. To our knowledge, we are the first to demonstrate the high prevalence of prediabetes (31.6%) in patients with cancer and its association with a 20% greater risk of MACE relative to normoglycemic individuals. We also provide novel data on MACE related to temporal changes to glycemic status in the prediabetes group, and our findings further establish its clinical relevance in patients who are prescribed ACT, whose numbers are expected to increase further because of the ageing population.

Both patients with diabetes and those with prediabetes have a higher risk of developing HF compared with individuals who have normal blood sugar levels. The combination of anthracycline exposure and metabolic conditions can lead to synergistic effects on cardiovascular health and a heightened risk of MACE events in these populations. The pathophysiologic mechanisms linking prediabetes/diabetes, HF, and MACE events are multifaceted. An abnormal glucose level can result in endothelial dysfunction, inflammation, and oxidative stress, which can lead to atherosclerosis, myocardial ischemia, and impaired cardiac function.[26,27] In the context of ACT, several additional mechanisms may further predispose hyperglycemic individuals to HF and related mortality. First, one of the mechanisms that underlies AIC is mitochondrial dysfunction and impaired ATP production,[28] which may cause further damage in the hyperglycemic state.[29] Second, ACT induces systemic insulin resistance, which is one of the major pathologies of diabetes,[30] and triggers massive cardiac glucose uptake.[31] Third, malignancy can negatively affect cardiac insulin signaling through the secretion of insulin-degrading enzymes, massive glucose adsorption, and reduced pancreatic insulin production. This further augments AIC via hyperglycemia.[29,32] Fourth, both AIC and HF are considered inflammatory diseases that may be intensified by impaired fasting glucose, contributing to a heightened

risk of clinical HF events.[33] Finally, patients with cancer are more likely to have preexisting diabetes than those without cancer.[34] These findings emphasize the importance of early detection and interventions to prevent the progression from prediabetes to diabetes and mitigate the risk of MACE in individuals with diabetes. The interaction between prediabetes/diabetes and anthracycline exposure remains incompletely understood and presents significant knowledge gaps that necessitate further research. Although the evidence described above suggests that the cardiotoxic effects of anthracyclines are compounded by the presence of metabolic conditions like prediabetes and diabetes, the precise mechanisms by which these conditions interact remain to be elucidated.

The relation between AIC and anthracycline dose is widely recognized. In subgroup analyses, our study has further demonstrated that the negative impact of hyperglycemia is more prominent in those who have received higher anthracycline doses, supporting the added detrimental effect when the two conditions occur simultaneously. Therefore, clinicians should exercise extra caution when treating patients with prediabetes/diabetes who have been exposed to high doses of anthracycline because they may be at greater risk for cardiac toxicity.[35]

It is worth noting that the risk of HF and mortality associated with glycemic status was higher among subgroups without baseline ACEI/ARB. Although the topic remains controversial, a recent meta-analysis suggested that ACEI/ARB may help preserve left ventricular systolic function in patients who receive anthracyclines.[36] It has been proposed that ACEI/ARB may prevent AIC through various mechanisms, including the inhibition of angiotensin II activity as well as anti-inflammatory and antioxidant effects.[37] Because both prediabetes and diabetes are associated with an increased risk of MACE, our subgroup analysis indicating a potential benefit from ACEI/ARB therapy in reducing the risk of MACE maybe of clinical relevance and warrants further investigation.

Prediabetes is a modifiable cardiovascular risk factor and can progress to overt diabetes in approximately 5%–10% of cases per year.[21] Among patients who had prediabetes, those who progressed to diabetes had a 50% excess risk of HF compared with those who remained prediabetic.[13] Our study reveals that minimizing the progression to diabetes in prediabetic patients who are prescribed ACT could reduce the subsequent risk of HF and all-cause mortality. Strategies to prevent or delay progression to overt diabetes are particularly important to reduce the burden of HF and mortality in patients receiving ACT. In the management of prediabetes in anthracycline-treated patients, a comprehensive approach is recommended. Lifestyle interventions (dietary changes, increased physical activity, and behavioral therapy), based on evidence from the Diabetes Prevention Program,[38,39] consistently reduced the risk of diabetes development in prediabetic individuals[21,25,40,41] and may help, although their impact on cardiovascular complications remains contentious.[42,43] Furthermore, metformin therapy might be a potential approach for such patients to improve their outcomes.[7,38] Clinicians should carefully consider the selection and dosing of anthracyclines, possibly opting for alternative agents with a lesser cardiotoxic profile or individualized dosing strategies to mitigate cardiotoxicity in prediabetic patients. The use of cardioprotective drugs like dexrazoxane, along with monitoring cardiac function during chemotherapy, may also offer additional benefits to those at increased cardiovascular risk in the management of prediabetes among anthracycline-treated patients.[7,44] In addition, the roles of insulin resistance, glucose adsorption changes, and mitochondrial dysfunction warrant an in-depth study to fully comprehend their contributions to AIC for establishing comprehensive clinical guidelines for monitoring, managing, and possibly preventing cardiotoxic effects in patients with prediabetes or diabetes who are undergoing chemotherapy with anthracyclines. To this end, large-scale, longitudinal studies and clinical trials are required to validate these potential intervention strategies and therapeutic targets. Considering its high prevalence and strong association with AIC, such as HF and mortality, prediabetes may represent a pivotal opportunity to prevent progression to overt diabetes and should be actively screened for in patients receiving ACT.

Study limitations

Several limitations of our study merit consideration. Echocardiographic data were not available in CDARS; thus, the differential impact of systolic and diastolic function could not be evaluated. Similar to other administrative databases, socioeconomic factors, smoking status at the index date, and lifestyle data are not systematically available. Several diabetes agents, such as SGLT2 inhibitors and GLP-1 receptor agonists, are known to reduce MACE. Although our study population did include patients who were receiving these agents, their numbers were negligible. Further studies that characterize these features may reveal additional pathophysiologic insights. Longitudinal anthropometric data are required to evaluate the independent association of glycemic changes with the risk of incident HF. Although data from patients who have visited private hospitals or have immigrated are not available, >90% of the local population is under the care of public hospitals and continue to be followed in this setting, with all their relevant data recorded by CDARS. Finally, residual confounders could remain despite using multivariable adjustment, such as symptoms and diabetes medicines. Whereas some diabetes medicines may be used for purposes other than treating diabetes, such as metformin for polycystic ovary syndrome, our study is focused primarily on the use of these medications in the context of diabetes management. This factor could potentially limit the generalizability or interpretation of our findings.

Conclusions

In this cohort of patients with cancer who received ACT, prediabetes was common and was associated with an increased risk of HF and mortality. The risk was amplified in those who progressed to overt diabetes compared with those who remained prediabetic. Therefore,

the optimal management of diabetes is vital to improve prognosis in these patients.

AUTHOR CONTRIBUTIONS

Iokfai Cheang: Conceptualization, data curation, formal analysis, investigation, and writing–original draft. **Xu Zhu**: Software, formal analysis, methodology, and visualization. **Jia-Yi Huang**: Conceptualization and writing–review and editing. **Yi-Kei Tse**: Writing–original draft and validation. **Hang-Long Li**: Writing–review and editing and validation. **Qing-Wen Ren**: Data curation and investigation. **Mei-Zhen Wu**: Data curation and investigation. **Yap-Hang Chan**: Investigation and project administration. **Xin Xu**: Data curation and investigation. **Hung-Fat Tse**: Project administration. **Ying Gue**: Investigation and supervision. **Gregory Y. H. Lip**: Investigation and supervision. **Xinli Li**: Visualization, resources, and project administration. **Kai-Hang Yiu**: Conceptualization, funding, validation, supervision, and project administration. All authors read and commented on the article, gave final approval, and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

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CONFLICT OF INTEREST STATEMENT

Gregory Y. H. Lip reports personal/consulting fees from Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo Company and Pfizer outside the submitted work. The remaining authors disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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