Doxorubicin-induced early-onset chronic progressive cardiotoxicity, pharmacogenetics and survival among breast cancer patients in Zimbabwe

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Background. Early-onset chronic progressive cardiotoxicity (ECPC) is a significant cause of morbidity and mortality among patients who receive doxorubicin-based chemotherapy for breast cancer.
Objective. To establish incidence of ECPC in black Zimbabwean women with breast cancer treated with doxorubicin and the resultant survival, and to describe the pharmacogenomic biomarkers' association with prognosis.
Method. A prospective observational study was conducted in Zimbabwe with 50 participants who received doxorubicin-based treatment and were actively followed up to 12 months, with 3-monthly echocardiography and vital status determined at 60 months for all-cause mortality analysis.
Results. ECPC was observed in 10% of participants. Median survival for participants who developed ECPC and those without was 11.9 v. 40.8 months. Participants with ECPC had 5-year overall survival (OS) of 0% v. 42% (hazard ratio (HR) 4.19, 95% confidence interval (CI) 1.27 - 13.79; p=0.018) for participants with no ECPC recorded. Median survival was significantly shorter for patients on calcium channel blockers (p=0.01). Cardiotoxicity, pre-existing hypertension and histological grade showed no significant association. Using multivariate analysis, poor OS was observed with ECPC (HR 4.19, 95% CI 1.27 – 13.79; p=0.018) and calcium channel blocker use (HR 2.38, 95% CI 1.07 - 5.32; p=0.034); no association was observed with pharmacogenomic biomarker risk categorisation based on *SLC28A3*, *UGT1A6* and *RARG* (HR 1.39, 95% CI 0.46 - 4.25; p=0.561).
Conclusion. Breast cancer patients with doxorubicin-induced ECPC had poorer OS. The risk of doxorubicin cardiotoxicity and poor survival could not be explained using *SLC28A3*-scoring pharmacogenomic profile. Breast cancer therapies with lower cardiotoxicity are needed in Zimbabwe and other low-resource settings.

Keywords: pharmacogenomics, anthracycline-induced cardiotoxicity, breast cancer survival, gene polymorphism

S Afr Med J 2026;116(5):e3655 https://doi.org/10.7196/SAMJ.2026.v116i5.3655

Breast cancer is the most common cancer among females in sub-Saharan Africa (SSA).[1] As SSA undergoes a transition in disease burden with increasing non-communicable disease incidence, both the incidence and mortality of breast cancer are increasing.[2] Africa has the highest mortality rate for breast cancer in the world, and this has been attributed to advanced disease stage at diagnosis, tumour biology, delayed intervention and inadequate treatment.[3] Cancer survival can also be significantly affected by treatment toxicity, timely management of these adverse events and genetic polymorphisms that affect toxicity risk.[4-6]

Management of breast cancer involves multimodal interventions that include surgery, chemotherapy, radiotherapy and hormonal therapy. The aim of cancer intervention is to maximise tumour control with minimum toxicity. For patients for whom chemotherapy is indicated, doxorubicin use is part of first-line treatment and doxorubicin-induced cardiotoxicity (DIC) is a dose-limiting concern.[7] DIC is categorised into *(i)* acute cardiotoxicity that occurs within the first week of anthracycline treatment, *(ii)* early-onset chronic progressive cardiotoxicity (ECPC) occurring <1 year after the completion of anthracycline treatment and *(iii)* late-onset chronic progressive cardiotoxicity whose onset occurs ≥1 year after the completion of anthracycline treatment.[8] Patients who develop DIC-related congestive heart failure have a poor prognosis, with mortality approaching >50% at 1 year.[9] Clinically, high risk factors for DIC include pre-existing hypertension, dyslipidaemia, diabetes mellitus, tobacco smoking and obesity.[10] At a genetic level, doxorubicin metabolism and protein transporter coding genetic polymorphisms have been shown to increase DIC risk. The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) recommends genotyping paediatric patients due to receive anthracycline-based chemotherapy for UDP-glucuronosyltransferase 1A6*4 (*UGT1A6**4-rs17863783), Solute carrier family 28 member 3 (*SLC28A3*-rs7853758) and Retinoic Acid Receptor Gamma (*RARG*-rs2229774) haplotypes to categorise more accurately DIC risk and to implement closer cardiac surveillance.[11] In a prospective cohort study in Zimbabwe, these pharmacogenomic biomarkers showed limited predictive value for direct DIC prediction.[12]

Concurrent medications may have cardioprotective effects against DIC.[13] In experimental animal model studies, calcium channel blockers used for hypertension resulted in preserved left ventricular function, elimination of toxicity-associated histopathologic

cardiomyocyte changes and reduction in observed cardiomyocyte apoptosis.[14-17] In addition, a meta-analysis of randomised controlled trials also reported significant DIC risk reduction in patients on concurrent statin therapy.[18,19] Other factors, including clinical stage at diagnosis, greatly affect prognosis and a recent study in Zimbabwe showed that 43% had distant metastases.[20] Various patient-specific and health system factors result in a higher proportion of patients presenting with stage IV disease at diagnosis.[21] Due to the unique challenges of disease presentation differences, stage at presentation, treatment intent, pharmacogenomic risk factors and reports of unique tumour biology in African populations, it is important to understand the cardiotoxicity and survival outcome association in breast cancer patients in an African setting like Zimbabwe.[22] The purpose of this study was to establish the incidence of ECPC and resultant 5-year survival outcome in breast cancer patients who received doxorubicin-based treatment at Zimbabwe's largest oncology centre.

Methods

Study design and participants

Between January 2019 and July 2020, a prospective cohort observational study was conducted at Parirenyatwa group of hospitals, Harare, Zimbabwe. Fifty participants above the age of 18 years with histologically confirmed invasive breast ductal or lobular carcinoma were recruited before doxorubicin-based chemotherapy was commenced as part of standard care for their diagnosis. Participants were recruited through convenience sampling, encompassing all indications for doxorubicin administration, including neoadjuvant, adjuvant and definitive therapy. Patients who had previous chest wall external beam radiotherapy, previous chemotherapy, who were non-black women or with abnormal left ventricular ejection fraction (LVEF) of <60% were excluded. The study received approval from the Medical Research Council of Zimbabwe ethics committee (MRCZ/A/2325). All participants provided written informed consent using MRCZ-approved forms, which outlined the study procedures and granted authorisation for the biobanking of blood specimens.

Data collection

Participants underwent cardiovascular assessment by a cardiologist using 2D echocardiography to measure LVEF at baseline and 3, 6, 9 and 12 months. Patients were actively followed in the study for up to 12 months after commencing doxorubicin-based chemotherapy treatment. Participants' demographics, comorbidities, chemotherapy doses, concurrent medications, examination findings and blood specimens for genotyping were collected.

Study endpoints

The endpoints for this study were incidence of ECPC and overall survival. A patient with ECPC was defined as having LVEF threshold of >10% reduction from the baseline echocardiography.[23,24] For overall survival, the participant's vital status at 60 months was obtained from the hospital records, and for participants who had died the date of death was recorded. Survival was determined from the day of enrolment into the study, which was at commencement of the doxorubicin treatment.

Pharmacogenomic biomarker testing

Genotyping was done using Genopharm®, an open Q15 array panel that contains 120 assays for over 48 genes.[12,25] Patients' DIC risk classification was based on copy number polymorphism detection system (CNPDS) recommendations into patients with *SLC28A3* rs7853758 A protective variant who do not carry *RARG* rs2229774 A or *UGT1A6* rs17863783 T alleles, as low genetic risk, or those carrying the *RARG* rs2229774 A or *UGT1A6* rs17863783 T risk variants, as high genetic risk; the rest of the patients were classified as moderate genetic risk.[11]

Statistical analysis

The data were analysed using Stata (version 18; Stata Corp, College Station, TX, USA) and R statistical software (version 3.4.3, https://www.r-project.org/). Categorical data were summarised using frequency counts and percentages and continuous variables were summarised with mean and standard deviation. Kaplan-Meier curve and log-rank test were used to assess visually the effect of categorical covariates on the time to death. Univariate and multivariate Cox regression models were used to assess the risk factors influencing the risk of death. A variable with p-value <20% at univariate Cox regression was considered for multivariate Cox regression. A backward elimination, with the help of likelihood ratio test at a p-value of 5%, was used to keep the variable in the final model.

Results

Twelve months after completion of doxorubicin-based chemotherapy, 5 (10%) participants developed ECPC and 45 (90%) did not. Median overall survival for participants who developed ECPC was 11.9 months, compared with 40.8 months in participants who did not develop ECPC, and the 5-year overall survival was 0% v. 42% respectively (hazard ratio (HR) 4.19, 95% confidence interval (CI) 1.27 - 13.79; p=0.018). The participant characteristics are summarised in Table 1. The median age at diagnosis of breast cancer was 44.6 v. 53.4 years in patients with ECPC and without ECPC, respectively.

Treatment

The mean cumulative doxorubicin dose was 235 (interquartile range (IQR) 57.62 - 376.30) mg/m^2 for the whole cohort – 235 mg/m^2 for participants who developed ECPC and 242 mg/m^2 for participants who did not develop ECPC. After chemotherapy, 15 (30%) participants received hormonal therapy with tamoxifen. The declared concurrent medications that the participants were taking at study enrolment are outlined in Table 2**.** No patients received trastuzumab treatment.

Survival

At 60 months, 20 (40%) participants were alive and 30 (60%) were deceased. Survival after enrolment into the study was compared for factor differences including tamoxifen treatment, pre-existing hypertension, ECPC occurrence, cancer group clinical stage, calcium channel blocker treatment and histological grading (Figs 1 - 6).

Univariate Cox regression analysis showed that compared with participants with ECPC, participants who did not have ECPC had a higher likelihood of overall survival (HR 2.9, 95% CI 1.1 - 7.62; p=0.031). Participants not taking any calcium channel blocker had a higher likelihood of overall survival compared with those receiving this treatment (HR 2.58, 95% CI 1.25 - 5.34; p=0.01). Both the ECPC and channel blocker treatment on multivariate analysis had significance in observed overall survival: HR 4.19 (95% CI 1.27 - 13.79; p=0.018) and HR 2.38 (95% CI 1.07 - 5.32; p=0.034), respectively.

Univariate analysis showed that moderate- and high-risk SLC28A3 scores had HR of 0.51 (95% CI 0.22 - 1.19; p=0.51) and 1.85 (95% CI 0.63 - 5.39; p=0.56), respectively. Patients who received tamoxifen after chemotherapy had a better overall survival (HR 0.44, 95% CI 0.18 - 1.07; p=0.071). However, univariate

Table 1. Demographic data and clinical characteristics of study participants with breast cancer

Characteristic	With ECPC *N*=5	Without ECPC *N*=45
Age (years), mean (range)	44.6 (28 - 66)	53.4 (29 - 77)
Cumulative doxorubicin dose (mg/m²), mean (range)	235 (60 - 360)	242 (120 - 376)
Health insurance, *n* (%)		
Yes	1 (25)	10 (22)
No	4 (75)	35 (78)
Family history of breast cancer, *n* (%)		
Yes	-	6 (13)
No	3 (60)	33 (73)
Unknown	2 (40)	6 (13)
On treatment for hypertension, *n* (%)		
Yes	4 (75)	25 (56)
No	1 (25)	20 (44)
History of smoking, *n* (%)		
Yes	-	2 (27)
No	5 (100)	43 (73)
HIV status, *n* (%)		
Yes	1 (25)	3 (7)
No	4 (75)	42 (93)
Histological subtype, *n* (%)		
Invasive ductal carcinoma	5 (100)	41 (91)
Invasive lobular carcinoma	-	4 (9)
Molecular subtypes, *n* (%)		
Her2-enriched	-	1 (2.2)
Luminal A	-	7 (15.6)
Luminal B	1 (20)	3 (6.7)
Triple-negative	1 (20)	5 (11)
Unknown	3 (60)	29 (64)
Clinical group stage, *n* (%)		
Stage II	0 (0)	5 (11)
Stage III	2 (40)	23 (51)
Stage IV	3 (60)	17 (38)

BMI = body mass index; BSA = body surface area; Her2 = Human epidermal growth factor receptor 2.

Table 2. Concurrent medications

Medicine	*N* (%)
Tamoxifen	
Yes	15 (30)
No	35 (70)
Calcium channel blockers	
Yes	16 (32)
No	33 (68)
Unknown	1 (2)
Beta-blockers	
Yes	6 (12)
No	43 (86)
Unknown	1 (2)
ACE/ARB inhibitors	
Yes	4 (8)
No	44 (88)
Unknown	2 (4)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

analysis showed insignificant association with cancer group stage and pre-existing hypertension (Table 3).

Discussion

In this study, 10% of participants developed ECPC and had a median survival of 11.9 months, compared with 40.8 months in participants who did not develop ECPC. The factors that significantly affected median survival in this study included ECPC, treatment with calcium channel blockers and tamoxifen therapy. DIC risk categorisation with pharmacogenomic *UGT1A6**4-rs17863783, *SLC28A3*-rs7853758 and *RARG*-rs2229774 haplotypes was not significantly associated with median survival.

The incidence of ECPC in this study is within range of other studies that have used a similar definition of a decrease in LVEF >10% from baseline on echocardiography within the first 12 months from treatment completion.[26-28] Although DIC risk after the first 12 months of chemotherapy still persists, the vast majority of DIC occurs in the first 12 months and this guided our study design.[27] DIC incidence has been reported to be three times higher in African-American patients compared with patients of European ancestry. This observation has multiple factors including the difference in prevalence of hypertension, diabetes and obesity, and other socioeconomic factors such as access to diagnostics and treatment.[29] Our study participants were all of black-African ancestry and were treated in a setting where routine echocardiography follow-up is not instituted. The ECPC incidence and resultant median survival we observed

Table 3. Univariate and multivariate Cox regression analysis for overall survival

	Univariate Cox regression analysis			Multivariate Cox regression analysis		
Parameter	**Hazard ratio (SE)**	***p*-value**	**95% CI**	**Hazard ratio (SE)**	***p*-value**	**95% CI**
ECPC	2.9 (1.43)	0.031	1.1 - 7.62	4.19 (2.55)	0.018	1.27 -13.79
Receiving calcium channel blocker	2.58 (0.96)	0.01	1.25 - 5.34	2.38 (0.98)	0.034	1.07 -5.32
SLC28A3 score						
Low risk	Reference			Reference		
Moderate risk	0.51 (0.22)	0.121	0.22 - 1.19	0.32 (0.16)	0.023	0.12 - 0.86
High risk	1.85 (1.01)	0.26	0.63 - 5.39	1.39 (0.79)	0.561	0.46 - 4.25
Cancer stages						
Cancer stage IV	Reference			-	-	-
Cancer stage III	0.82 (0.30)	0.587	0.39 - 1.70	-	-	-
Cancer stage II	0.00001 (0.0001)	1.00	-	-	-	-
Tamoxifen use	0.44 (0.2)	0.071	0.18 -1.07	-	-	-
With hypertension	1.89 (0.74)	0.108	0.87 - 4.09	-	-	-

SE = standard error of the estimates; CI = confidence interval; ECPC = early-onset progressive cardiotoxicity.

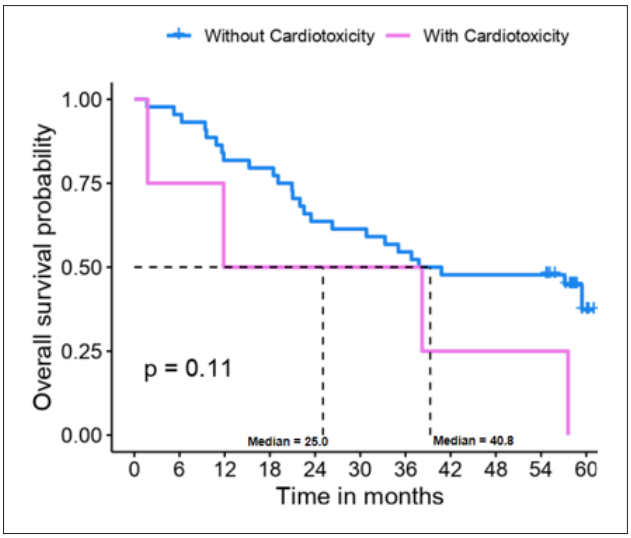

Fig. 1. Kaplan-Meier curve for study participants comparing survival based on participants with cardiotoxicity (ECPC) v. without cardiotoxicity (ECPC), median survival 11.9 v. 40.8 months (p=*0.11*).

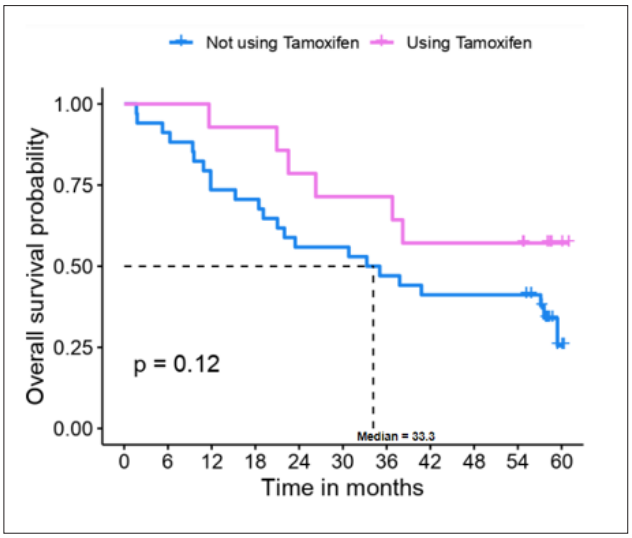

Fig. 3. Kaplan-Meier curve for participants with oestrogen receptor-positive cancer receiving tamoxifen v. not receiving tamoxifen, median survival 33.3 months v. median survival not reached at 60 months (p=*0.12*).

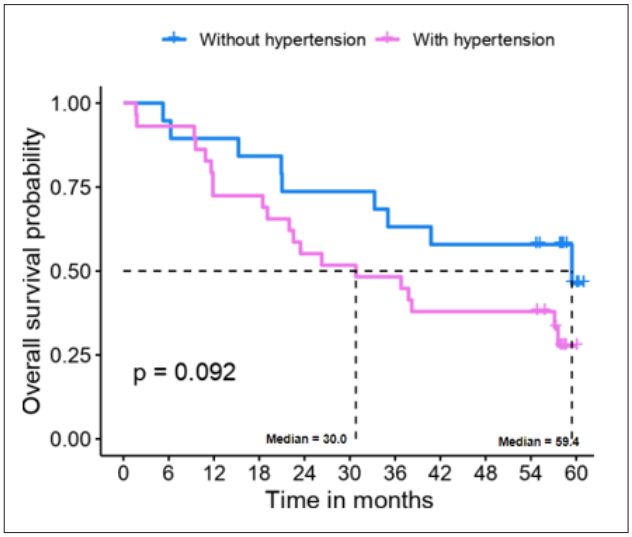

Fig 2. Kaplan-Meier curve for participants with hypertension v. without hypertension diagnosis, median survival 22.5 v. 59.4 months (p=*0.09*).

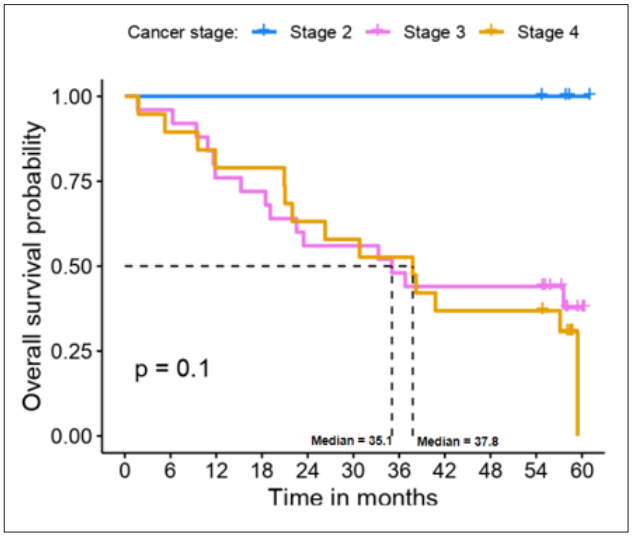

Fig. 4. Kaplan-Meier curve for participants by clinical cancer stage median survival, stage II not reached at 60 months, stage III = 35.1 months and stage IV = 37.8 months (p=*0.1*).

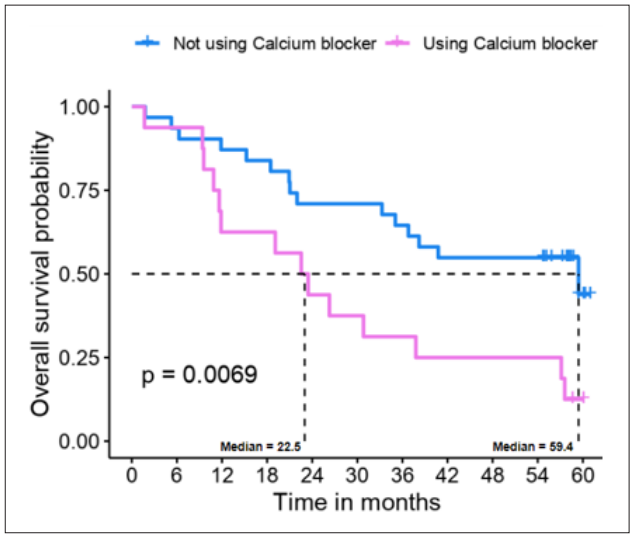

Fig. 5. Kaplan-Meier curve for participants using calcium channel blocker v. not using calcium channel blocker treatment, median survival 22.5 v. 59.4 months (p=*0.01).*

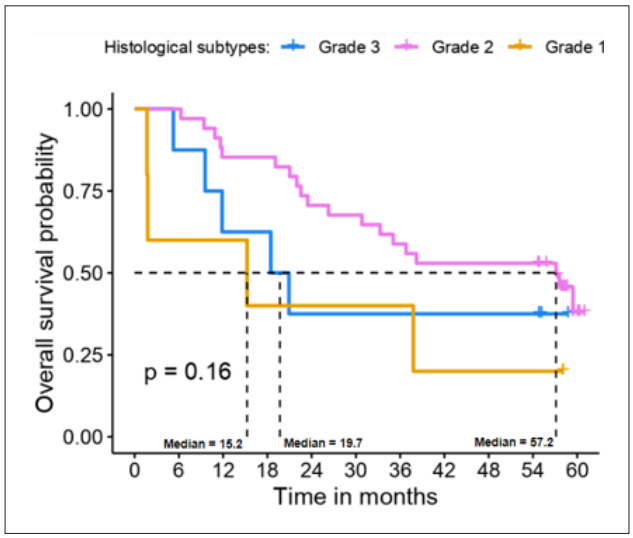

Fig 6. Kaplan-Meier curve for histological subtypes (tumour grade), median survival grade 1, grade 2 and grade 3 of 15.2 months, 57.2 months and 19.7 months, respectively (p=*0.16).*

adds to the evidence that follow-up echocardiography is important. The National Comprehensive Cancer Network and American Society of Clinical Oncology recommend that echocardiography every 6 - 12 months is undertaken after completion of doxorubicin-based chemotherapy.[30]

The observed median survival for all participants was 37.8 months. Unfortunately, due to a lack nationwide breast cancer screening to enable early diagnosis in Zimbabwe, most women have stage III and stage IV disease and this has been demonstrated in previous reports.[20,31] Most cancer patients in low- and middle-income countries such as Zimbabwe present with advanced-stage disease, which confers a poor prognosis, and other factors associated with this are limited knowledge about the disease, and delayed diagnosis and treatment.[32,33] The survival findings from other African regional countries have shown a similar cancer stage distribution and poor prognosis; however, none have reported the association of treatment toxicity such as ECPC.[34-38]

Various risk factors have been described for DIC, including pre-existing hypertension, age, sex, ethnicity and co-medications.[39,40] In this study, we report that participants with pre-existing hypertension had a lower median survival than those with no history of hypertension; however, this association was not significant. In addition to these findings, participants who were on treatment with calcium channel blockers had a significantly higher risk of death. This finding on calcium channel blockers is contrary to some reports by other researchers. In these studies, it is hypothesised that blockade of L-type calcium channel (LTCC) attenuates DIC development via the favourable regulation of calcium/calmodulin-dependent protein kinase II.[41] Experimental animal studies have shown that utilising nifedipine blocking or gene knockdown of LTCC suppresses doxorubicin-related cardiomyocyte cellular injury, ameliorating the risk of DIC.[42] One source that could result in inconsistent findings contrary to this hypothesis could be the observed polymorphism in $Ca_v1.2$ encoding the alpha-1 subunit of the LTCC, resulting in possible lack of the protective effect.[43]

Pharmacogenetic biomarker-guided cancer interventions form a significant component of precision oncology.[44,45] The CPNDS recommendations for genotyping patients for *UGT1A6**4-rs17863783, *SLC28A3*-rs7853758 and *RARG*-rs2229774 are for paediatric patients. In this study, we are reporting the observed effect of the classification of these biomarkers on survival among adult breast cancer patients of black-African ancestry. No significant association was noted in this cohort; this is in keeping with previous findings of the limited positive predictive value for DIC.[12] Further research is required on predicting this important treatment-related event, given the survival implications of occurrence.

In our study, hormonal therapy with tamoxifen, cancer group stages II and III, and histological grade showed insignificant survival association. At 60 months, median survival was not reached for patients who received tamoxifen, in keeping with the inherent favourable prognosis that oestrogen receptor-positive breast cancer infers.[46,47] Breast cancer staging in this study cohort and generally in SSA may be inaccurate due to challenges to accessing advanced imaging due to level of development.[6,20,48] The limited access to advanced imaging may result in the understaging of some patients. This limited access to advanced imaging for all patients has been accepted and addressed in the effort to harmonise the National Comprehensive Cancer Network (NCCN) cancer management guidelines for SSA, guiding practitioners according to locally available resources. These guidelines do recommend chest radiograph and ultrasound scan-based staging when other more accurate modalities are not available.[49]

The limitations of our study include a small sample size, lack of analysis of specific cause of death and the use of genotyping for specific pharmacogenomic variants only. Further studies need a larger sample size based on the ECPC event incidence we observed, specific cause of death verification and genetic sequencing for gene variant signal detection. The observed incidence of ECPC and resultant survival provides a basis for exploring implementation of echocardiography-based follow-up after doxorubicin treatment. Another option could be the use of less cardiotoxic chemotherapy options such as epirubicin or liposomal doxorubicin, although a limiting factor here could be the upfront drug cost challenges.[50] However, the lower cardiotoxicity of these two drugs, myelosuppression of liposomal doxorubicin and avoided echocardiography costs could ultimately make these alternatives a cost-viable option.[51-53]

Conclusion

In this study, breast cancer patients who received doxorubicin-based chemotherapy and developed ECPC had poorer survival compared with patient who did not develop ECPC. Patients on treatment with calcium channel blockers had significantly poorer median survival and the study-observed median survival was not significantly associated with current pharmacogenomic biomarkers for DIC in this group of black Zimbabwean patients.

Declaration. The study was approved by the ethics committee of the MRCZ (MRCZ/A/2325). All study participants signed an MRCZ-approved informed consent form detailing the study and approving biobanking of blood specimens. All elements of the study were performed in accordance with the Declaration of Helsinki and the relevant regulations and laws governing research in Zimbabwe.

Data availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgements. The late James Hakim (MB ChB, FRCP), Professor of Medicine, Faculty of Medicine and Health Sciences, University of Zimbabwe, contributed to the design and implementation of the study. Mrs Patricia Gambiza, who was the project manager and followed through the study to its intended completion.

Author contributions. TM: study design, data collection, data analysis, interpretation, writing of the manuscript; VN: study design, laboratory analysis, data collection, data analysis, interpretation, writing and reviewing manuscript; MB: study design, project management, project supervision, manuscript review; CM: study design, project management, project supervision, funding, manuscript review; TF: study design, data analysis, project management, project supervision, funding, manuscript review; TBC: study design, data analysis, project management, project supervision, funding, manuscript review; NN: study design, project management, project supervision, manuscript review.

Funding. Support for this work was provided through grant funding from the Regents of the University of Colorado (University of Colorado, Denver) (grant number FY18.276.002) and the National Cancer Institute (NCI) USA (grant number 5P20CA210677), the European & Developing Countries Clinical Trials Partnership (grant number TMA2016SF-1508) and the Bill and Melinda Gates Foundation (BMGF) (grant number ID INV-036801).

Conflict of interest. None.

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Received 19 May 2025; accepted 24 November 2025.