

A Comparison of Factors Associated with Breast Cancer Stage at Diagnosis and 2-year Overall Survival Pre and During Covid-19 Periods in Johannesburg, South Africa

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Abstract

Purpose: COVID-19 affected care access, treatment options, and cancer outcomes. We assessed stage at diagnosis and 2-year overall survival among South African women with breast cancer (BC) pre- (1 January 2017 to 31 December 2018) and during COVID-19 (01 April 2020 to 31 March 2022).

Methods: 1772 participants were enrolled at two Johannesburg academic hospitals, 978 pre- and 794 during COVID-19. Cox proportional hazard models examined risk factors of mortality.

Results: Late-stage (III+IV) diagnosis increased by 7% during COVID-19. Two-year crude survival was 72.4% overall. Diagnosis during COVID-19 decreased mortality risk (Hazard ratio (HR)=0.71, 95% Confidence Interval (CI): 0.58-0.87).

A family history of BC protected against late-stage diagnosis during both periods. Pre-COVID-19, unemployment (OR=1.47 95%CI 1.07-2.03) and household poverty (OR=1.37 95% CI 1.03-1.82) and being single during COVID-19 increased late-stage odds (OR=1.31 95%CI 1.05-1.62).

Being unemployed increased mortality risk (HR=1.36, 95%CI: 1.09-1.69 pre-COVID-19; HR=1.43, 95%CI: 1.06-1.93 COVID-19) as did poor education pre-COVID-19 and tobacco use during COVID-19 (HR=1.60, 95% CI:1.10-2.33).

Late-stage BC increased mortality risk (HR = 2.65, 95%CI: 1.95-3.61 pre-COVID; HR = 1.81, 95%CI: 1.31-2.51 COVID) as did high tumor proliferation rates (Ki67 $\geq 20\%$) (HR=1.53, 95%CI: 1.22-1.91 pre-COVID; HR = 1.43, 95%CI: 1.03-2.00 COVID). BC subtypes during the pandemic, HR-/HER2+ (HR=1.59, 95%CI: 1.04-2.42) and TNBC (HR=1.60, 95%CI: 1.16-2.19) and positive HIV status pre-COVID (HR=1.61, 95%CI: 1.28-2.02) increased mortality risk. Versus surgery as first treatment, no treatment and neoadjuvant modalities increased mortality risk.

*Conclusions:*Health system and socioeconomic factors negatively impacted access to care; HIV and cancer treatment changes during COVID-19, contributed to improved 2-year survival.

Introduction

COVID-19 caused major disruptions to society and healthcare systems worldwide [1]. In South Africa (SA), access to cancer diagnostics and treatments within the Public Health System was limited by travel restrictions and hospital bed and staff shortages [2]. Staff from outpatient departments (OPD) were reassigned to non-patient contact areas based on risk profile or placed in self-quarantine due to exposure or infection, leading to significant staff shortages. Diagnostic procedures were limited because of restrictions on radiological and other diagnostic investigations, necessitating altered referral and triaging processes, with elective surgical procedures for cancer patients delayed to prioritize resources to cope with the pandemic [3, 4]. As a consequence, the number of newly diagnosed cases of BC decreased by 10% between 2019 and 2020, per the South African National Cancer Registry [5].

Many high-HDI countries also reported pandemic-related reductions in BC screening and diagnosis volumes, and increased proportions of advanced-stage BC [6–8]. In addition, a recent USA study reported a modest, negative impact of COVID-19 on BC survival[9].

BC stage at diagnosis and treatment quality are major determinants of survival. In the USA, where population-based mammography screening is available, the Surveillance, Epidemiology, and End Results (SEER) program reported that 66% of women were diagnosed with localized and very early-stage breast cancer, and in combination with state-of-art treatments ensured that the 5-year overall survival rates between 2014 and 2020 were 99.6% for localized cancers, 86.7% for regional cancers and 31.9% for distant or late-stage cancers, and 69.7% for unknown or un-staged cancers[10]. In contrast, for SSA, including SA, where BC incidence and mortality rates are steadily increasing [11], and population-based mammography screening is not always available, 50–65% of cancers are diagnosed at advanced stage (III/IV) [12, 13]. Being Black, having less than secondary education, a lack of BC knowledge, and low-income jobs are associated with delayed diagnosis [13]. Consequently, SSA has more than double the age-standardized breast cancer mortality-to-incidence rate ratios than those of high HDI settings [14]

Guided by the biopsychosocial theoretical model [15], we aimed to compare health system, sociodemographic, clinical, lifestyle risk and treatment factors associated with stage at diagnosis and 2-year overall survival rates among SA women with invasive BC before and during the pandemic. To our knowledge, such reports for SA and SSA have not been published.

Materials and methods

Study setting

This longitudinal cohort study enrolled 1,772 women newly diagnosed with invasive BC over 24-month periods between 1 January 2017 and 31 December 2018 (pre-COVID-19) and 1 April 2020 and 31 March 2022 (during COVID-19). Periods were selected to avoid treatment and overall survival assessment overlaps. The participants were enrolled at Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) as previously described [15]. These hospitals serve urban and peri-urban communities that reside within 65 km from the hospitals [12]. CHBAH is the referral hospital for three million people in Soweto and eastern and southern regions neighboring Johannesburg. CMJAH serves around five million people from central Johannesburg and eastern and western neighboring regions. They receive referrals from primary health clinics and via secondary hospitals in neighboring regions and provide full cancer diagnostic and treatment services. BC is usually diagnosed at a symptomatic stage because BC screening is not formalized in the public health system. Patients received diagnostic assessments, including clinical staging, diagnostic ultrasound and mammography imaging, and immunohistopathological diagnosis and receptor subtyping from core biopsies. Multimodal cancer treatments, including surgery, chemotherapy, immune therapy, radiation therapy, and endocrine treatments, were provided as previously described [16]. Pre-COVID-19, CHBAH provided only surgical and endocrine treatments, and BC patients had to travel to the CMJAH for

chemotherapy, immune therapy and radiation treatments. During the pandemic, chemotherapy services were initiated at CHBAH in April of 2021, which increased its diagnostic and treatment load without expansion of theatre time, nursing and pathology capacity. In April of 2021, a fire at the CMJAH halted cancer treatment services for 4 months; BC patients from CMJAH received their chemotherapy and immune therapy treatments at CHBAH, with radiation oncology treatments provided at an Academic Hospital 60 km away. Treatment services resumed at CMJAH in July 2021, with neoadjuvant treatments prioritized to mitigate surgery constraints.

Recruitment and Data Collection

Participants provided written informed consent and were enrolled if they were female, at least 18 years old, newly diagnosed with invasive BC (stage 1–4). As shown in Fig. 1, pre-pandemic (36) and 71 during COVID-19 of 1879 women were excluded, 90 with in situ cancer, 4 with phyllodes tumors, and 13 with incomplete diagnostic, treatment, and follow-up data. Participants were clinically staged using the 7th edition of the American Joint Committee on Cancer (AJCC)[12]. Data were collected by trained study staff as previously reported[15]: Self-reported socioeconomic and demographic factors, behavioral risk factors, and clinical and tumor factors and treatment information were collected from medical records as previously described [17, 18]. BC knowledge and residential distance to the treatment hospitals were assessed as previously described [17, 19]. Receptor subtyping was determined by immunohistopathology. Luminal A was defined using Allred scoring [20] as estrogen receptor (ER) or progesterone receptor (PR)-positive, Human Epidermal Growth Factor Receptor 2 (HER2)-negative, and with Ki67 proliferation index $\leq 15\%$; luminal B was defined as ER+/PR+ HER2-negative and with Ki67 $> 15\%$ and ER+/PR+ HER2 + any Ki67%. Equivocal scores were resolved by FISH testing. ER+/or PR + are regarded as Hormone receptor (HR) positive. HER2-enriched subtypes were defined as ER-/PR- HER2 + and triple negative as ER-/PR- HER2-. For Ki67 proliferation indices, $\leq 20\%$ were defined as low risk and Ki67 $\geq 20\%$ as high risk.

Data Management and Analysis

Risk factors were stratified by enrolment period (pre- and during COVID-19) for analysis. Frequency distributions were used to describe characteristics of the study participants. We compared determinants of stage at BC diagnosis, using a binomial logistic regression model. In multivariate logistic regression models, odds ratios (ORs) were examined in five individual risk-specific models plus a combined fully adjusted model, for associations with stage at BC diagnosis. Survival analyses were performed from date of pathologically confirmed diagnosis to the earliest date of death or two years after follow-up (whichever came first). Cox proportional hazards were modeled in a stepwise fashion to examine risk factors of death. All risk factors were combined in a final, fully adjusted model (for each enrolment group and the total cohort). Analyses were performed using Stata 18.5 (StataCorp Ltd, Texas, USA) with $p < 0.05$ values indicating statistically significant differences.

Results

Breast cancer risks among study cohort by enrolment periods

Of 1,772 participants, 55.2% were enrolled pre- and 44.8% during COVID-19. During the pandemic, more patients were enrolled at CHBAH (73.4% vs 59.7%), and more individuals came from economically vulnerable households. Unemployment and single relationship status remained high across both periods; breast cancer knowledge declined during COVID-19; and proportions of HIV-positive individuals increased (26.8% vs 21.9%). Late-stage BC diagnoses increased by 7% during the pandemic. Treatment patterns shifted, with increased use of primary endocrine therapy (13.1% vs 6.9%) and surgical treatments decreased (31.4% vs 40.8%). (Table 1).

Table 1
Comparison of risk categories of breast cancer in the SABCHO Cohort Pre-and during COVID-19 Periods

Exposure domain N (%)	Time period		
	Pre-COVID	COVID	Total
Total sample size of cohort at enrolment	978 (55.2)	794 (45.8)	1772
Enrolment hospital			
CHBAH	584 (59.7)	583 (73.4)	1167 (65.9)
CMJAH	394 (40.3)	211 (26.6)	605 (34.1)
Household & sociodemographic vulnerability and risk			
Age at diagnosis:			
Mean (SD)	54.9 (14.6)	53.4 (13.3)	54.2 (14.0)
Minimal social support (cohabiting vs single):			
Relationship status: Single (including divorced and widowed)	586 (59.9)	458 (57.7)	1044 (59.8)
Missing	3 (0.3)	6 (0.8)	9 (0.5)
Employment status (employed vs unemployed):			
Unemployed (including retired and students)	684 (69.9)	582 (73.3)	1266 (71.4)
Missing	2 (0.2)	1 (0.1)	3 (0.2)
Education level (secondary or higher vs primary or less):			
Primary school or less (R0/G7 + informal)	242 (24.7)	144 (18.1)	386 (21.8)
Missing			4 (0.2)
Household poverty (high wealth score vs low to middle wealth score):			
Low to Mid wealth index score (0–3)	409 (41.8)	484 (61.0)	893 (50.4)
Missing	1 (0.1)	2 (0.3)	3 (0.2)
Family member diagnosed with cancer:			
Yes	118 (12.1)	99 (12.5)	217 (12.2)
Missing	30 (3.1)	25 (3.1)	55 (3.1)
Abbreviations: CHBAH (Chis Hani Baragwanath Academic Hospital), CMJAH (Charlotte Maxeke Johannesburg Academic Hospital), SD (Standard deviation.), IQR (Interquartile range), HR (Hormone receptor)			

Exposure domain N (%)	Time period		
	Pre-COVID	COVID	Total
Knowledge of breast cancer (good vs poor to intermediate):			
Poor to intermediate (score 0–5)	446 (45.6)	495 (62.3)	941 (53.1)
Missing	5 (0.5)	6 (0.8)	11 (0.6)
Distance from Residence to Hospital (km)			
Mean (SD)	26.1 (44.1)	25.5 (34.5)	25.9 (40.1)
Median (IQR)	18.9 (8.4–32.7)	20.1 (8.7–33.2)	19.6 (8.5–32.8)
Missing	1 (0.1)	15 (1.9)	16 (0.9)
Multi-morbidity burden:			
One or more comorbidities (including diabetes, hypertension, heart disease, stroke and morbid obesity)	560 (57.3)	425 (53.5)	985 (55.6)
Median (IQR)	1 (0–1)	1 (0–1)	1 (0–1)
Behavioral risk			
Tobacco smoking:			
Yes	121 (12.4)	71 (8.9)	192 (10.8)
Missing	2 (0.2)	1 (0.1)	3 (0.2)
Clinical risks			
HIV status at time of breast cancer diagnosis:			
Positive	214 (21.9)	213 (26.8)	427 (24.1)
Missing	12 (1.2)	17 (2.1)	29 (1.8)
Stage at diagnosis:			
Stage 1 + 2	442 (45.2)	304 (38.3)	746 (42.1)
Stage 3 + 4	536 (54.8)	490 (61.7)	1026 (57.9)
Cancer proliferation risk:			
High: Ki67 ≥ 20%	674 (68.9)	562 (70.8)	1236 (69.8)
Abbreviations: CHBAH (Chis Hani Baragwanath Academic Hospital), CMJAH (Charlotte Maxeke Johannesburg Academic Hospital), SD (Standard deviation.), IQR (Interquartile range), HR (Hormone receptor)			

Exposure domain N (%)	Time period		
	Pre-COVID	COVID	Total
Missing	43 (4.4)	43 (5.4)	86 (4.9)
Receptor subtype risk			
HR+/HER2-	547 (55.9)	411 (51.8)	958 (54.1)
HR+/HER2+	171 (17.5)	128 (16.1)	299 (16.9)
HR-/HER2+	62 (6.3)	55 (6.9)	117 (6.6)
HR-/HER2-	164 (16.8)	145 (18.3)	309 (17.4)
Missing	34 (3.5)	55(6.9)	89 (5.0)
Treatment risks			
First Treatment			
Never Treated	113 (11.6)	98 (12.3)	211 (11.9)
Primary Endocrine	67 (6.9)	104 (13.1)	171 (9.7)
NACT (Neoadjuvant chemotherapy)	399 (40.8)	339 (42.7)	738 (41.6)
Surgery	399 (40.8)	249 (31.4)	648 (36.6)
Palliative DXT only	0	4 (0.5)	4 (0.2)
Abbreviations: CHBAH (Chis Hani Baragwanath Academic Hospital), CMJAH (Charlotte Maxeke Johannesburg Academic Hospital), SD (Standard deviation.), IQR (Interquartile range), HR (Hormone receptor)			

Insert Table 1.

Table 1 *Comparison of risk categories of breast cancer in the SABCHO Cohort Pre-and during COVID-19 Periods*

Factors associated with late-stage breast cancer in women diagnosed pre- and during COVID-19

Combined multiple logistic regression models (adjusted for all risk factors) were assessed for associations with late-stage BC by period and the combined cohort (Table 2). Individual models (1-enrolment hospital, 2-household & socio-demographics, 3-behavioural factors, 4-clinical and 5-age risk) are presented in Supplementary Tables 1 and 2. Pre-COVID-19, factors significantly increasing odds of late-stage BC diagnosis were enrolment at CMJAH compared to CHBAH (OR = 1.92, 95%CI: 1.45–2.54, $p < 0.01$), unemployment (OR = 1.47, 95%CI: 1.07–2.03, $p = 0.018$), lower household wealth (OR = 1.37, 95%CI: 1.03–1.82, $p = 0.033$). Increasing age was modestly protective (OR = 0.98, 95%CI: 0.97–0.99, $p <$

0.01). Having a family member diagnosed with BC was protective (OR = 0.63, 95%CI: 0.42–0.95, p = 0.029).

Table 2

Multivariate logistic regression analysis of factors associated with breast cancer stage at diagnosis among participants stratified by period of enrolment

Period of enrolment	Pre-COVID-19 1 Jan 2017- 31 Dec 2018	COVID-19 1 Apr 2020 -31 Mar 2022	Total Combined
Variables	OR (95%CI) P-value	OR (95%CI) P-value	OR (95%CI) P-value
Pandemic			
Pre-COVID-19			1 (ref)
COVID-19			1.44 (1.17–1.77) <0.01
Enrolment hospital			
CHBAH	1 (ref)	1 (ref)	1 (ref)
CMJAH	1.92(1.45–2.54) <0.01	1.39 (0.96–2.02) 0.08	1.71 (1.37–2.14) <0.01
Household & sociodemographic			
Social support			
In a relationship	1 (ref)	1 (ref)	1 (ref)
Single (including divorced and widowed)	1.08 (0.81–1.43) 0.61	1.67 (1.20–2.33) 0.02	1.31 (1.05–1.62) 0.02
Employment status			
Employed	1 (ref)	1 (ref)	1 (ref)
Unemployed (including retired and students)	1.47 (1.07–2.03) 0.02	1.34 (0.93–1.94) 0.12	1.41 (1.11–1.79) 0.01
Education level			
Secondary or higher	1 (ref)	1 (ref)	1 (ref)
Primary school or less	1.32 (0.93–1.87) 0.12	1.31 (0.984–2.05) 0.23	1.32 (0.93–1.87) 0.12
Household wealth			
High wealth index score	1 (ref)	1 (ref)	1 (ref)
Ref = reference category, 95% CI in parenthesis, significant p-value (< 0.05) shown in bold face			
Abbreviations: CI = Confidence Interval; CHBAH = Chris Hani Baragwanath Academic Hospital; CMJAH = Charlotte Maxeke Johannesburg Academic Hospital			

Period of enrolment	Pre-COVID-19 1 Jan 2017- 31 Dec 2018	COVID-19 1 Apr 2020 -31 Mar 2022	Total Combined
Variables	OR (95%CI) P-value	OR (95%CI) P-value	OR (95%CI) P-value
Pandemic			
Low-mid wealth index score (0–3)			
Family member diagnosed with breast cancer			
No	1 (ref)	1 (ref)	1 (ref)
Yes			
Knowledge of breast cancer			
Good (score 6–7)	1 (ref)	1 (ref)	1 (ref)
Poor-intermediate (score 0–5)			
Distance from residence to hospital (km)			
Multimorbidity burden			
Delays before presenting to hospital (days)			
Behavioral risk factors			
Tobacco smoking			
No	1 (ref)	1 (ref)	1 (ref)
Yes			
Clinical risks			
HIV status at time of breast cancer diagnosis			
Negative	1 (ref)	1 (ref)	1 (ref)
Positive			
Age at diagnosis	0.98 (0.97–0.99) 0.01		
Ref = reference category, 95% CI in parenthesis, significant p-value (< 0.05) shown in bold face			
Abbreviations: CI = Confidence Interval; CHBAH = Chris Hani Baragwanath Academic Hospital; CMJAH = Charlotte Maxeke Johannesburg Academic Hospital			

During COVID-19 the effect of socioeconomic variables diminished, with only social support (being single: OR = 1.671, 95%CI: 1.20–2.33, $p < 0.01$) and family history of BC (OR = 0.54, 95%CI: 0.35–0.85, $p = 0.01$) remaining significant. The pandemic may thus have attenuated structural disparities while amplifying the role of individual-level factors in shaping diagnostic outcomes.

Two-year overall survival of women diagnosed with breast cancer in Johannesburg.

Of the 1,772 women followed up at 2-years, 912(51.5%) had died (57.0% pre- and 44.7% during COVID-19). The median age of deceased women was 55 (44–66) years pre-COVID-19 and 54 (43–64) years during the pandemic. The 2-year crude overall survival was 72.4% (70.2–74.4) for the entire cohort; 71.4% (68.4–74.1) pre- and 73.7% (70.4–76.7) during COVID-19, showing a slightly higher overall survival estimate of 2.3% for women diagnosed during COVID-19. Age- standardized net survival estimates were higher during COVID-19 at 79.2% (75.3–82.5) vs 76.0% (73.6–79.0) (Table 3).

Table 3
Information on follow-up, deaths and survival estimates by COVID period

Period	Pre-COVID	COVID	Total
Number of women followed up N (%)	978(55.2%)	794(44.8%)	1772(100.0%)
Median time since diagnosis (range), years	2.0 (1.6-2.0)	2.0 (1.3-2)	2.0 (1.5-2.0)
Status at end of follow-up			
Died	557(57.0%)	355(44.7%)	912(51.5%)
Administrative censoring at 2 years	409(41.8%)	386(48.6%)	795(44.9%)
Administrative censoring before 2 years	12(1.2%)	53(6.7%)	65(3.7%)
Number of deaths during the period since diagnosis, years			
0 to < 1	154(27.6%)	101(28.5%)	255(28.0%)
1 to < 2	124(22.3%)	71(20.0%)	195(21.4%)
= 2	279(50.1%)	154(43.4%)	433(47.5%)
Median age (IQR) of deceased patients during the 2-year follow-up period	55 (44–66)	54 (43–64)	54 (44–65)
1-year survival			
Crude survival	84.2% (81.7–86.3)	83.8% (81.0–86.2)	84.0% (82.2–85.6)
Net survival	86.7% (84.1–88.8)	87.6% (84.8–89.9)	87.1% (85.2–88.7)
Age-standardized net survival	86.4% (83.7–88.7)	87.0% (83.8–89.6)	86.7% (84.7–88.5)
2-year survival			
Crude survival	71.4% (68.4–74.1)	73.7% (70.4–76.7)	72.4% (70.2–74.4)
Net survival	75.8% (72.7–78.7)	79.1% (75.7–82.1)	77.3% (75.0–79.4)
Age-standardized net survival	76.0% (73.6–79.0)	79.2% (75.3–82.5)	77.4% (74.9–79.6)
Data are n (%) or percentage surviving (95% CI) unless otherwise indicated.			

Insert Table 2

Table 2 Multivariate logistic regression analysis of factors associated with breast cancer stage at diagnosis among participants stratified by period of enrolment

Insert Table 3

Table 3 Information on follow-up, deaths and survival estimates by COVID period

Factors associated with 2-year overall survival among women diagnosed with breast cancer in Johannesburg.

Table 4 presents the fully adjusted Cox proportional hazards models assessing factors associated with 2-year overall survival pre- and during COVID-19 and for the total cohort. Individual risk models by enrolment period are presented in supplementary tables 3 and 4. Enrolment during COVID-19 was associated with improved survival (HR = 0.71, 95%CI: 0.58–0.87). Clinical characteristics and treatment patterns emerged as the strongest predictors of mortality. Women diagnosed with late-stage BC experienced substantially higher mortality (HR = 2.65, 95%CI:1.95–3.61 pre- and HR = 1.81, 95% CI: 1.31–2.51 during COVID-19) and this effect was higher pre-COVID-19. Tumour subtype was also associated with mortality: HR+/HER2 + BC was linked to high risk of death pre- (HR = 1.39, 95%CI: 1.10–1.74), and during COVID-19 (HR = 1.46, 95%CI: 1.06-2.00). HR-/HER2+ (HR = 1.59, 95%CI: 1.04–2.42) and TNBC (HR = 1.60, 95%CI: 1.16–2.19) were associated with worse survival during COVID-19 only. Similarly, high tumor proliferation index rate (Ki67 ≥ 20%) was significantly associated with worse survival (HR = 1.53, 95% CI:1.22–1.91 pre-COVID; HR = 1.43, 95%CI: 1.03-2.00 COVID). Positive HIV status was linked to higher mortality pre-COVID only (HR = 1.61, 95%CI: 1.28–2.02). During COVID there was a change in ARV regimen from FDC -a single tablet triple therapy of tenofovir (TDF), emtricitabine (FTC) and efavirenz to triplet tenofovir disoproxil fumarate-lamivudine, dolutegravir (TLD).

Table 4

Multivariate Cox Proportional Hazards Regression analysis of factors associated with 2-year overall survival among participants stratified by period of enrolment

Period of enrolment	Pre-COVID-19 1 Jan 2017-31 Dec 2018	COVID-19 1 Apr 2020-31 Mar 2022	Total Combined
Variables	HR (95%CI) P-value	HR (95%CI) P-value	HR (95%CI) P-value
Pandemic			
Pre-COVID-19			1 (ref)
COVID-19			1.44 (1.17–1.77) <0.01
Enrolment hospital			
CHBAH	1 (ref)	1 (ref)	1 (ref)
CMJAH	1.92(1.45–2.54) <0.01	1.39 (0.96–2.02) 0.08	1.71 (1.37–2.14) <0.01
Household & sociodemographic			
Social support			
In a relationship	1 (ref)	1 (ref)	1 (ref)
Single (including divorced and widowed)	1.08 (0.81–1.43) 0.61	1.67 (1.20–2.33) 0.02	1.31 (1.05–1.62) 0.02
Employment status			
Employed	1 (ref)	1 (ref)	1 (ref)
Unemployed (including retired and students)	1.47 (1.07–2.03) 0.02	1.34 (0.93–1.94) 0.12	1.41 (1.11–1.79) 0.01
Education level			
Secondary or higher	1 (ref)	1 (ref)	1 (ref)
Primary school or less	1.32 (0.93–1.87) 0.12	1.31 (0.984–2.05) 0.23	1.32 (0.93–1.87) 0.12
Household wealth			
High wealth index score	1 (ref)	1 (ref)	1 (ref)
Ref = reference category, 95% CI in parenthesis, significant p-value (< 0.05) shown in bold face			
Abbreviations: CI = Confidence Interval; CHBAH = Chris Hani Baragwanath Academic Hospital; CMJAH = Charlotte Maxeke Johannesburg Academic Hospital			

Period of enrolment	Pre-COVID-19 1 Jan 2017-31 Dec 2018	COVID-19 1 Apr 2020-31 Mar 2022	Total Combined
Variables	HR (95%CI) P-value	HR (95%CI) P-value	HR (95%CI) P-value
Pandemic			
Low-mid wealth index score (0–3)	0.85(0.71–1.03) 0.11	0.88(0.69–1.12) 0.29	0.94(0.79–1.13) 0.53
Family member diagnosed with breast cancer			
No	1 (ref)	1 (ref)	1 (ref)
Yes	0.95(0.72–1.27) 0.74	0.80(0.55–1.16) 0.24	0.80(0.60–1.06) 0.12
Knowledge of breast cancer			
Good (score 6–7)	1 (ref)	1 (ref)	1 (ref)
Poor-intermediate (score 0–5)	0.85(0.70–1.02) 0.08	0.83(0.65–1.05) 0.12	0.87(0.73–1.04) 0.12
Distance from residence to hospital (km)	1.00(1.00–1.00) 0.52	1.00(1.00–1.00) 0.85	1.00(1.00–1.00) 0.76
Multimorbidity burden	0.97(0.80–1.18) 0.77	0.87(0.69–1.11) 0.27	0.91(0.76–1.09) 0.32
Behavioral risk factors			
Tobacco smoking			
No	1 (ref)	1 (ref)	1 (ref)
Yes	1.13(0.86–1.47) 0.38	1.60(1.10–2.33) 0.01	1.45(1.12–1.88) 0.01
Clinical risks			
HIV status at time of breast cancer diagnosis			
Negative	1 (ref)	1 (ref)	1 (ref)
Positive	1.61(1.28–2.02) < 0.01	1.16(0.88–1.533) 0.28	1.24(1.01–1.53) 0.04
Ref = reference category, 95% CI in parenthesis, significant p-value (< 0.05) shown in bold face			
Abbreviations: CI = Confidence Interval; CHBAH = Chris Hani Baragwanath Academic Hospital; CMJAH = Charlotte Maxeke Johannesburg Academic Hospital			

Period of enrolment	Pre-COVID-19 1 Jan 2017-31 Dec 2018	COVID-19 1 Apr 2020-31 Mar 2022	Total Combined
Variables	HR (95%CI) P-value	HR (95%CI) P-value	HR (95%CI) P-value
Pandemic			
Stage at diagnosis			
Stage I + II	1 (ref)	1 (ref)	1 (ref)
Stage III + IV	2.65(1.95–3.61) < 0.01	1.81(1.31–2.51) < 0.01	2.56(1.97–3.34) < 0.01
Cancer proliferation index			
Ki67 < 20%	1 (ref)	1 (ref)	1 (ref)
Ki67 ≥ 20%	1.53(1.22–1.91) < 0.01	1.43(1.03-2.00) 0.03	1.64(1.30–2.07) < 0.01
Receptor subtype			
HR+/HER2-	1 (ref)	1 (ref)	1 (ref)
HR+/HER2+	1.39(1.10–1.74) 0.01	1.46(1.06-2.00) 0.02	1.37(1.09–1.72) 0.01
HR-/HER2+	1.05(0.74–1.51) 0.78	1.59(1.04–2.42) 0.03	1.33(1.00-1.81) 0.07
HR-/HER2+	1.23(0.95–1.58) 0.11	1.60(1.16–2.19) < 0.01	1.54(1.23–1.93) < 0.01
First treatment received effects			
Surgery	1 (ref)	1 (ref)	1 (ref)
No treatment	4.50(3.17–6.38) < 0.01	10.71(6.85–16.76) < 0.01	8.39(6.07–11.59) < 0.01
Primary endocrine	1.81(1.16–2.82) 0.01	3.64(2.24–5.90) < 0.01	2.81(1.92–4.11) < 0.01
Neoadjuvant chemotherapy	1.13(0.80–1.58) 0.50	1.99(1.31–3.01) < 0.01	1.43(1.05–1.96) 0.03
Palliative radiotherapy		3.76(1.10-12.79) 0.03	2.65(0.81–8.69) 0.11
Ref = reference category, 95% CI in parenthesis, significant p-value (< 0.05) shown in bold face			
Abbreviations: CI = Confidence Interval; CHBAH = Chris Hani Baragwanath Academic Hospital; CMJAH = Charlotte Maxeke Johannesburg Academic Hospital			

Period of enrolment	Pre-COVID-19 1 Jan 2017-31 Dec 2018	COVID-19 1 Apr 2020-31 Mar 2022	Total Combined
Variables	HR (95%CI) P-value	HR (95%CI) P-value	HR (95%CI) P-value
Pandemic			
Age at diagnosis	0.98 (0.97–0.99) 0.01	1.00(0.99–1.02) 0.43	1.00(0.99–1.01) 0.62
Ref = reference category, 95% CI in parenthesis, significant p-value (< 0.05) shown in bold face			
Abbreviations: CI = Confidence Interval; CHBAH = Chris Hani Baragwanath Academic Hospital; CMJAH = Charlotte Maxeke Johannesburg Academic Hospital			

Treatment-related factors had the most profound impact, with absence of treatment associated with a 4.5-fold increase in hazard pre-COVID and a 12.8-fold increase during COVID (HR = 4.50, 95%CI: 3.17–6.38 pre-COVID; HR = 10.71, 95%CI: 6.85–16.76 COVID). Women who received endocrine as first treatment (often associated with old age or frailty), were at higher risk of mortality (HR = 1.81, 95%CI: 1.16–2.82 pre-COVID; HR = 3.64, 95%CI: 2.24–5.90 during COVID). Similarly, during COVID-19, neoadjuvant chemotherapy and palliative radiotherapy as first treatments associated with higher mortality risk relative to surgery as first treatments received,

Being unemployed was also associated with poor survival (HR = 1.36, 95%CI: 1.09–1.69 pre-and HR = 1.43, 95%CI: 1.06–1.93 during COVID-19). Having only primary education or less was linked to 1.5-fold increase in hazard pre-COVID-19 and during COVID-19 tobacco use was associated with higher odds of death (HR = 1.60, 95%CI:1.10–2.33).

Insert Table 4

Table 4: *Multivariate Cox Proportional Hazards Regression analysis of factors associated with 2-year overall survival among participants stratified by period of enrolment*

Discussion

In this prospective comparison of women receiving BC care at two academic hospitals in Johannesburg before and during COVID-19, we observed two seemingly divergent patterns: an increase in late-stage diagnosis during COVID-19, alongside improved crude 2-year overall survival. These findings align with the broader international literature showing that pandemic-era disruptions preferentially reduced screening and diagnostic throughput, altered referral pathways, and reshaped treatment sequencing; however, they also highlight that short-term survival metrics can be influenced by substantial selection and case-mix changes during system shocks. Globally, systematic reviews consistently report large declines in cancer screening, diagnostic procedures and incident diagnoses during the first pandemic

waves, with the greatest disruptions often occurring in settings with fewer reserves and longer pre-existing queues[21].

Stage at diagnosis: structural access constraints interacting with individual vulnerability

We observed a 7% absolute increase in late-stage BC at diagnosis in the combined cohort during COVID-19. This direction of effect is consistent with findings from a systematic review in high- HDI settings where reductions in breast biopsy recommendations and cancer diagnoses were driven predominantly by reduced screening-linked detection rather than symptomatic presentation, a mechanism that would be expected to shift the stage distribution toward more advanced disease if sustained. Variable recovery trajectories and frequent backlog effects were also reported[6].

In SA, where most BC is diagnosed symptomatically and pathways already involve substantial pre-diagnostic and pre-treatment delays, pandemic restrictions plausibly intensified the “last mile” barriers that determine whether symptoms translate into diagnosis. The Groote Schuur Hospital experience in Cape Town, SA documented material reductions in diagnostic and surgical service volumes and identified patient-reported reasons for delayed care that are directly relevant to urban SA settings - pandemic fear, travel restrictions, isolation requirements and constrained transport availability - reinforcing that demand-side and supply-side constraints co-occurred[4, 20]. At a SSA regional level, pervasive interruptions across diagnostic, surgical, radiotherapy and systemic therapy services were reported, often compounded by workforce redeployment, stockouts, curtailed clinic time, and reduced patient attendance due to movement restrictions and infection risk perception[6].

Hospital-level effects: institutional pathways and resource gradients

Across periods, enrolment hospital was an important determinant of stage at diagnosis, consistent with facility-level gradients in diagnostic capacity, referral efficiency, and “time-to-tissue” performance. Before COVID-19, women diagnosed at CMJAH had approximately double the odds of late-stage disease compared with CHBAH, which may reflect systematic differences in catchment areas, primary-to-tertiary referral pathways, imaging/biopsy capacity, or queue dynamics for surgical and pathology services. During COVID-19, this hospital effect attenuated, plausibly because the pandemic imposed a shared “ceiling” of constrained access across sites (e.g., patient travel constraints, reduced outpatient throughput, and diagnostic bottlenecks), thereby homogenising barriers that were previously more institution specific. This interpretation is coherent with multi-country descriptions of pandemic disruptions in which system-wide restrictions and service reprioritisation dominated over usual local variation in pathways[21].

Socioeconomic vulnerability: attenuation during COVID-19 as a “universal barrier” or selection phenomenon

A notable finding was the attenuation of socioeconomic gradients in late-stage diagnosis during COVID-19. Two interpretations merit emphasis. First, COVID-19 restrictions and economic shocks may have created a “universal barrier” environment in which transport, safety, clinic access and competing household demands deteriorated across socioeconomic strata, compressing differences that are typically observed. Second, and perhaps more plausibly in facility-based cohorts, this pattern may signal **selection into care**: during severe access constraints, the subset of women who successfully reached tertiary services may be systematically different from those who did not—potentially reducing observable SES gradients in the attending population even if true population-level inequities worsened. This possibility aligns with global data indicating that service interruptions were frequently most severe in medium-HDI contexts and among populations dependent on public-sector services or long travel distances[21].

Social support and family history as consistent protective factors

Social support and family history of BC remained protective across both enrolment periods. Internationally, social connectedness and prior exposure to cancer in family networks are linked to symptom appraisal, cancer literacy, and navigation capability; during crises, these factors may become even more salient as they can reduce decisional delay and mobilise practical resources (transport funds, childcare, accompaniment). Evidence from LMIC-focused reviews of BC care during COVID-19 highlights that where formal systems are stressed, informal networks and patient agency become particularly influential in determining whether women persist through disrupted pathways[22].

Treatment adaptations and pathway reconfiguration during COVID-19

Consistent with global patterns, we observed a shift toward greater use of neoadjuvant chemotherapy and primary endocrine strategies during COVID-19, likely compensating for curtailed surgical services availability. Across high-, middle- and low-resource settings, breast cancer management during COVID-19 frequently adopted: (i) increased reliance on neoadjuvant systemic therapy (including endocrine “bridging”), (ii) prioritisation frameworks for surgery, and (iii) expanded hypofractionated radiotherapy to reduce facility visits[8]. Real-world evidence suggests that short-term pre-operative endocrine therapy (typically ≤ 3 months) can be safe and tolerable for appropriately selected hormone receptor-positive patients, supporting its role as a crisis strategy—although longer-term oncologic consequences require ongoing evaluation[23].

Two-year survival: interpreting improved short-term outcomes under pandemic conditions

We found that crude and age-standardised 2-year survival was higher for enrolment during COVID-19, with ~ 30% lower odds of mortality. This contrasts with widespread concern—supported by modelling and observational service data—that COVID-19-related delays could increase cancer mortality over subsequent years. Several non-mutually exclusive mechanisms could explain improved **short-term** survival in our cohort:

1. *Selection into diagnosis and treatment:* During COVID-19, barriers to accessing tertiary oncology care were unusually high. Women who succeeded in reaching care may have had greater health-seeking agency, fewer unmeasured comorbidities, stronger social support, or better capacity to adhere to altered treatment schedules, factors that could improve short-term survival independent of tumour biology. This phenomenon has been highlighted as a key interpretive challenge when comparing pre/post COVID clinical cohorts, because the denominator (who presents and is captured) changes[24].
2. *Treatment prioritisation effects:* Under crisis conditions, multidisciplinary teams often triaged more aggressively, prioritising higher-risk patients for systemic therapy initiation and modifying sequencing to avoid long waits. International studies report increased use of neoadjuvant strategies and more streamlined decision-making during acute phases, which could plausibly improve early mortality if it reduces time-to-treatment in biologically aggressive disease[25].
3. *Short follow-up horizon:* A 2-year window may be insufficient to capture the downstream survival penalty of diagnostic delays, backlogs, and stage migration—particularly for hormone receptor-positive subtypes where survival differences often emerge later. Consequently, improved 2-year survival does not preclude worse 5-year outcomes for the broader population, especially if COVID-19 generated a “missing cohort” of undiagnosed women who present later.
4. *Differentiating exposure effects:* It is not possible to differentiate effects associated with COVID-19 itself from those associated with the temporary CMJAH closure caused by the fire and the new chemotherapy facility established at CHBAH, both which occurred during the COVID-19 enrolment period.

HIV and survival: plausibility of ART-era effects and need for caution in attribution

In the pre-COVID period, HIV infection was adversely associated with 2-year survival, but this effect attenuated during COVID-19. Our findings of improved odds of survival during COVID-19 may be attributed to the antiretroviral (ARV) treatment switch to the dolutegravir containing regime, implemented in 2019, shortly before the onset of COVID-19[26]. The change in ARV treatment regimen was based on evidence indicating higher viral suppression rates and lower resistance development compared to prior treatment options in routine-care contexts [27]. This finding warrants cautious interpretation. Firstly, HIV-associated differences in BC survival in Southern Africa appear to persist in several contemporary cohorts, even under ART availability, and are influenced by stage, treatment completion, multimorbidity, and structural vulnerability. Second, ART switching is unlikely to be the sole driver of the observed

pattern; COVID-era selection into care and differential mortality ascertainment could also reduce apparent HIV effects. ART changes may thus have been one of the contributing factors that may have improved background health and treatment tolerance among women with HIV. We acknowledge that more direct measures (viral load trajectories, ART adherence, cancer treatment dose intensity and delays) would be needed to attribute causality.

Implications

- *Protect diagnostic throughput (“time-to-tissue”) as a resilience metric.* The stage shift observed during COVID-19, together with international evidence on reduced biopsies and diagnostic volumes, indicates that protecting core diagnostic services during crises should be a priority (e.g., ring-fenced imaging/biopsy slots, rapid pathology, and decentralised assessment where feasible).
- *Institution-level quality improvement to reduce unwarranted variation.* The persistent effect of enrolment hospital pre-COVID suggests actionable differences in pathways (referral friction, clinic-to-biopsy intervals, surgical queues). Facility-level dashboards tracking time intervals (symptom-to-first-contact, first-contact-to-biopsy, biopsy-to-treatment) would enable targeted QI at higher-risk sites.
- *Embed navigation and social protection linkages in oncology pathways.* Economic vulnerability and limited support predicted poorer outcomes. COVID-era evidence from South Africa and SSA underscores that transport constraints and fear of infection materially suppress care seeking. Patient navigation (including CHW-linked models), transport vouchers, and integrated social work support should be treated as core components of breast cancer care rather than optional add-ons.
- *Formalise evidence-based crisis treatment protocols.* The observed rise in neoadjuvant systemic therapy aligns with international “phase-based” triage guidance and the broad adoption of bridging endocrine therapy and radiotherapy to maintain treatment continuity with fewer facility visits. Standardised emergency protocols could reduce ad hoc variation during future disruptions.
- *Integrate BC symptom triage with high-coverage platforms (HIV/NCD care).* The protective effect of cancer experience and the potential HIV-ART era improvements support the logic of integrating breast symptom awareness and referral pathways within routine HIV and chronic disease services, where women may already have established healthcare contact and trust.

Key strengths include the prospective design, high data completeness, and low loss to follow-up, enabling robust estimation of associations with stage and 2-year survival. Limitations include: (i) potential selection bias during COVID-19, as women facing the greatest barriers may not have reached tertiary care and thus are under-represented; (ii) reliance on some self-reported measures, introducing misclassification risk; (iii) limited generalizability beyond these academic centers and their referral networks; and (iv) the relatively short follow-up horizon, which may under-detect long-term survival consequences of COVID-era delays, particularly for less aggressive subtypes; and v) that one cannot differentiate specific exposure effects.

In conclusion, within Johannesburg’s public-sector oncology context, the COVID-19 period was associated with a modest shift toward later-stage BC diagnosis but paradoxically improved 2-year survival—likely reflecting a combination of altered treatment sequencing, care prioritization, ART-era improvements among women with HIV, and selection into care under extreme access constraints. These findings underscore that safeguarding diagnostic and treatment continuity, reducing institutional pathway variation, and embedding navigation and social protection are central to equitable breast cancer outcomes and to health-system resilience during future shocks.

Abbreviations

COVID

19-coronavirus disease

DCIS

ductal carcinoma in situ

HIV

Human Immunodeficiency Virus

NACT

neoadjuvant chemotherapy

Palliative DXT

Palliative Radiotherapy

CHBAH

Chris Hani Baragwanath Academic Hospital

CMJAH

Charlotte Maxeke Johannesburg Academic Hospital

DSTI

NRF-Department of Science, Technology and Innovation and the National Research Foundation

HDI

Human Development Index

HREC

Human Research Ethics Committee Medical

SABCHO

South African Breast Cancer and HIV Outcomes Study

Declarations

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Competing interests

Alfred Neugut: Otsuka, United Biosource Corp, Hospira, Value Analytics, Merck, Organon, and GlaxoSmithKline (Consulting/advisory relationship); EHE Intl (Scientific Advisory Board); Otsuka (Research Funding); Paul Ruff: Merck, Roche, Pfizer, GSK, Jansen, AstraZeneca, ImmunityBio, Amgen (clinical trial funding to the institution). The other authors indicated no relevant financial or non-financial interests to disclose.

Author contributions

Olaide O. Ojoniyi: Conceptualisation; methodology; data curation; investigation; validation; formal analysis; data visualisation; writing – original draft; writing – review and editing. *Wenlong Carl Chen*: Data curation; investigation; validation; formal analysis; writing – review and editing; project administration. *Rebaone Petlele*: Writing – review and editing; validation. *Raylton P. Chikwati*: Writing – review and editing; validation. *Monica E. Akokuwebe*: Writing – review and editing; validation. *Nivashini Murugan, Phumudzo Ndwambi, Jennifer Edge, Neo Helen Selwane*: Data curation, writing-review and editing; *Alfred I Neugut*: Funding acquisition, writing -review and editing; *Herbert Cubasch*: Funding acquisition, writing-review and editing, *Paul Ruff*: Funding acquisition, writing-review and editing, *Shane Norris*: supervision; conceptualisation, writing – review and editing, *Maureen Joffe*: Funding acquisition; supervision; conceptualisation, writing – review and editing; project administration. All authors reviewed and approved the manuscript before submission for publication

Data availability statement

All statistical findings are documented within this publication. The Stata do-files used for the analyses are accessible from Olaide O Ojoniyi (first author) upon reasonable request.

Ethics approval

This research was approved by the University of the Witwatersrand Human Research Ethics Committee (Medical), (M1911203), the University of KwaZulu-Natal Biomedical Research Committee (BF080/15),

and the Institutional Review Board of Columbia University (IRB-AAAQ135). All participants provided written informed consent to participate in the study and for the publication of their de-identified data.

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Figures

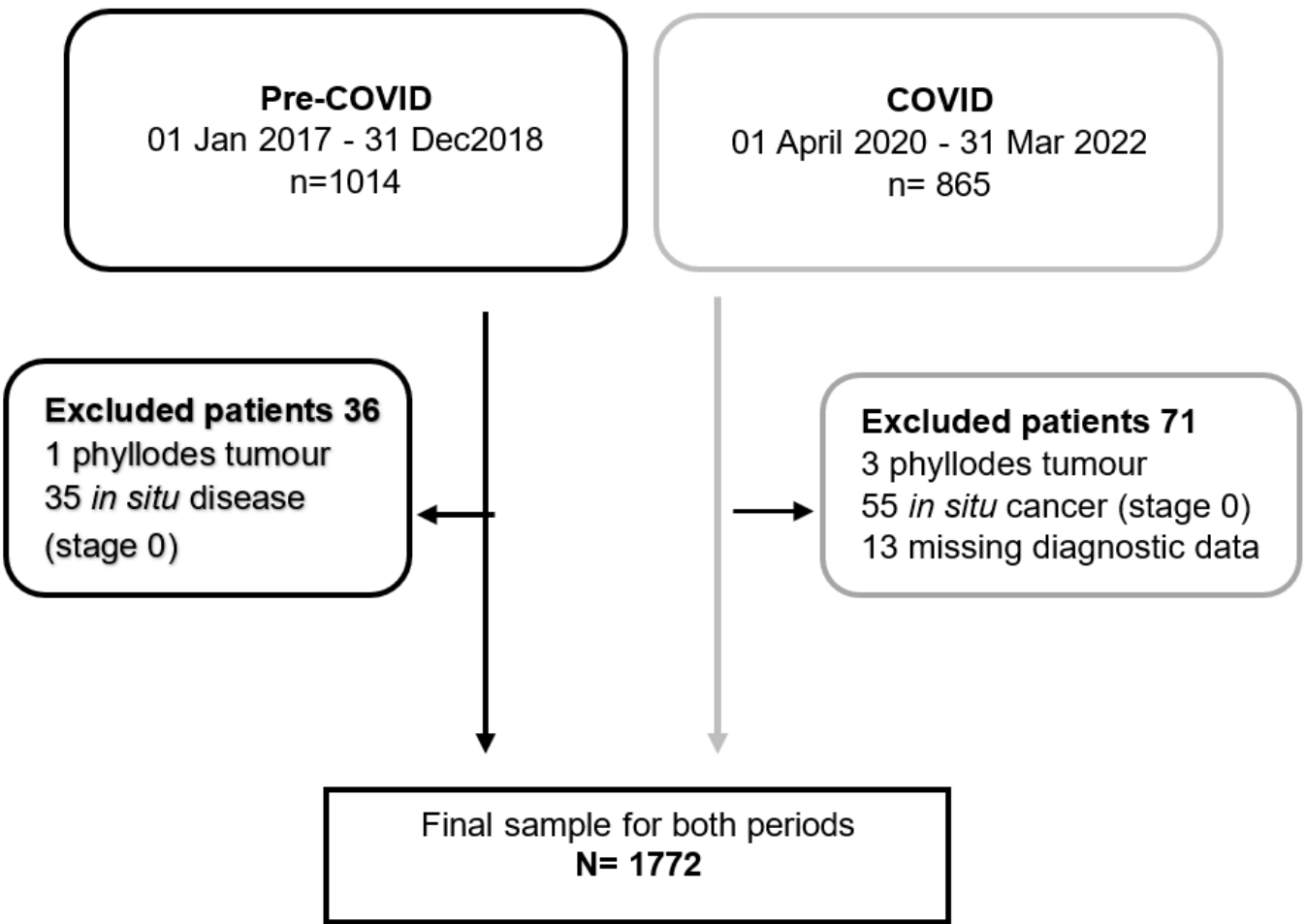


Figure 1

Participant accrual flowchart

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