Overall Survival and Economic Impact of Triple-Negative Breast Cancer in Brazilian Public Health Care: A Real-World Study

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ABSTRACT

PURPOSE Triple-negative breast cancer (TNBC) presents notable treatment difficulties, especially in the public health care systems of low- and middle-income countries where access to advanced therapies is restricted. This study investigates TNBC's clinical, epidemiologic, and economic effects on survival within Brazil's public health care system.

METHODS We conducted a retrospective cohort study of patients with TNBC treated between 2010 and 2019. Overall survival (OS) rates by stage were analyzed across various patient groups, including those receiving neoadjuvant or adjuvant treatment, patients with or without complete pathologic response, Black and non-Black patients, and those treated with or without carboplatin-based therapy. Cox proportional hazards models were applied to estimate hazard ratios (HRs) with 95% CIs, and annual treatment costs were calculated per stage.

RESULTS Among 1,266 patients with TNBC, 710 met eligibility criteria. Kaplan-Meier analysis indicated stage II patients had a 47% lower mortality risk than stage III (HR, 0.53 [95% CI, 0.33 to 0.85]; $P = .009$). Patients in the adjuvant treatment group had a reduced risk (HR, 0.48 [95% CI, 0.34 to 0.69]) compared with the neoadjuvant group. Achieving complete pathologic response (pCR) greatly improved OS (HR, 0.21 [95% CI, 0.11 to 0.43]; $P < .001$). Black patients had better survival rates than non-Black (HR, 0.58 [95% CI, 0.40 to 0.86]; $P = .006$). Carboplatin use did not significantly affect OS (HR, 0.96 [95% CI, 0.65 to 1.43]; $P = .857$). The average monthly cost for systemic TNBC treatment increased with disease progression, from $101.87 in US dollars (USD) for stage I to $314.77 USD for stage IV second-line therapy.

CONCLUSION This study provides insight into TNBC in Brazil's public health system, showing that OS decreases with disease progression but is higher among Black patients. pCR and adjuvant therapy improve survival, although costs increase significantly at advanced stages, highlighting the economic burden of late-stage TNBC management.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

Triple-negative breast cancer (TNBC) is a highly aggressive subtype with a poorer prognosis compared with other breast cancer subtypes.[1] It is defined by the absence of estrogen and progesterone hormone receptors and a lack of human epidermal growth factor receptor 2 (HER2) receptor amplification.[2] Globally, TNBC accounts for approximately 15% of breast cancer cases, with higher incidence rates in Latin America and sub-Saharan Africa compared with slightly lower rates in Asia and Europe.[3] In Brazil, the AMAZONA study identified TNBC as the second most prevalent breast cancer subtype among adults, predominantly affecting younger patients.[4,5]

The financial burden of managing TNBC is substantial, especially in resource-limited settings. Global direct annual medical costs for TNBC range from $20,000 in US dollars (USD) for stages I-III to $300,000 USD for stage IV.[6] In Brazil, this burden is compounded by frequent hospital

CONTEXT

Key Objective

To evaluate the clinical outcomes and economic burden of triple-negative breast cancer in Brazil's public health care system, examining survival factors and costs associated with various treatment approaches.

Knowledge Generated

Patients achieving a pathologic complete response and receiving adjuvant treatment demonstrated improved survival. The study found no survival benefit with carboplatin use and identified higher survival among Black patients.

Relevance

Findings highlight the importance of early intervention and pCR as a treatment goal, with potential implications for improving survival outcomes and cost management in resource-limited health care settings.

admissions and emergency room visits.[7] A study of 3,000 patients in the private health care system found that early and locally advanced TNBC costs averaged $7,351.72 USD per patient per month (PPPM), rising to $10,005.95 USD PPPM for metastatic TNBC.[7]

Chemotherapy remains the standard treatment for TNBC because of the absence of hormone or HER2 receptors, which renders endocrine and HER2-targeted therapies ineffective.[8] Common chemotherapeutic agents include anthracyclines and taxanes,[3] with treatment (adjuvant or neoadjuvant) tailored to individual risk assessments. Despite this, responses are often short-lived, with over 50% of patients relapsing within 3-5 years of diagnosis.[9] Median overall survival (OS) for metastatic TNBC ranges from 10.2 months in real-world data (RWD) to 18.7 months in clinical trials, with 5-year survival rates of 65% for regional metastases and 11% for distant metastases.[10,11]

Recent advancements have significantly transformed TNBC treatment. Poly(ADP-ribose) polymerase (PARP) inhibitors, immunotherapy, and antibody-drug conjugates (ADCs) have shown promise. Immunotherapies such as atezolizumab and pembrolizumab have demonstrated efficacy in PD-L1–positive metastatic TNBC,[12,13] while pembrolizumab combined with chemotherapy has become a standard in neoadjuvant settings, improving pathologic complete response (pCR) and disease-free survival.[14-16] Sacituzumab govitecan, an ADC, has extended progression-free survival and OS in metastatic TNBC,[17] and PARP inhibitors such as olaparib have improved outcomes in *BRCA*-mutated advanced and early-stage TNBC.[18,19]

However, these advancements may not yet be widely applicable in low- and middle-income countries such as Brazil, where access to innovative therapies in the public health care system remains limited. In Brazil's public system, chemotherapy continues to be the primary treatment for nonsurgical TNBC, with 84% of patients relying on public health care.[4,5] These disparities underscore the importance of RWD studies. Defined by the US Food and Drug Administration as data routinely collected on patient health and health care delivery,[20] RWD provides critical insights into TNBC treatment and outcomes in resource-constrained settings. This study aims to leverage RWD to comprehensively analyze TNBC within Brazil's public health care system, offering valuable insights into the challenges and outcomes of managing this aggressive cancer subtype.

This study examines the clinical, epidemiologic, and economic TNBC parameters in Brazil's public health care system using RWD, focusing on OS. It evaluates survival rates by stage and treatment type, OS disparities by ethnicity, with emphasis on Black patients, and the correlation between complete pathologic response and OS. It also assesses the effectiveness of carboplatin regimens and calculates the direct costs of TNBC treatments.

METHODS

Study Design and Sources of RWD

This real-world study involved a retrospective analysis of structured medical records from consecutive patients treated at Pérola Byington Hospital, nowadays known as Hospital da Mulher in São Paulo, Brazil, between 2010 and 2019. This study was conducted in accordance with the reporting oncology real-world evidence[21] studies guidelines by the European Society for Medical Oncology.[22] Detailed documentation of all data manipulations, including the rationale for excluding a small number of patients (0.7%) because of missing or incomplete data, was meticulously maintained, as illustrated in Figure 1. Breast cancer staging was performed following the American Joint Committee on Cancer guidelines, specifically using the 8th edition of the American Joint Committee on Cancer Staging Manual.[23]

Ethical approval was obtained from the Women's Health Reference Center's institutional ethics committee (Hospital Pérola Byington) under CAAE number 72387317.6.0000.0069.

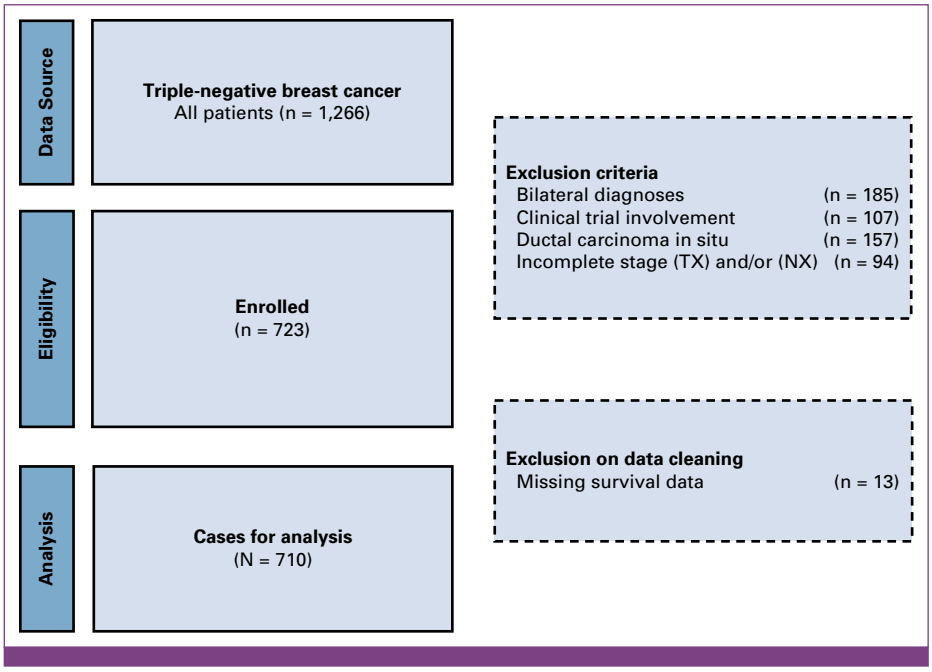

FIG 1. Participant enrollment flowchart.

The Institutional Review Board of Pérola Byington Hospital approved the use of patient data before study commencement. Informed consent was waived, ensuring ethical compliance and patient confidentiality.

Eligibility Criteria

The study included female patients age 18 years or older with stages I-IV TNBC, treated at Pérola Byington Hospital, São Paulo, Brazil. Only those with complete staging information who received treatment were included. Exclusions applied to patients with other breast cancer subtypes, multiple diagnoses, previous clinical trial participation, or bilateral breast cancer.

Variables of the Study

Clinical and epidemiologic data were collected for patients with TNBC, including age, cancer stage, nodal status, tumor size, diagnosis and treatment timelines, prescribed adjuvant or neoadjuvant therapies, hospitalization duration, adverse events, and mortality. OS was defined as the interval from treatment initiation to death or last follow-up.

Direct treatment costs were estimated by analyzing prescription counts and systemic regimen details for each TNBC stage from Pérola Byington Hospital, contextualized within the Brazilian public health care system.

Statistical Analysis

To assess normality, the distributions of descriptive variables were evaluated using histograms and normal probability plots. Continuous variables were summarized by central tendency and dispersion (mean or median, standard deviation, or interquartile range) on the basis of normality, while categorical variables were described by frequency. Multivariate analysis was performed using a Cox proportional hazards model for key variables.

OS was analyzed by clinical stage, treatment type, ethnicity, and pathologic response. OS was defined as the time in months from diagnosis to death for patients with a recorded death. Patients without a recorded death or with follow-up dates before diagnosis were excluded. Kaplan-Meier survival curves, evaluated with the log-rank test, assessed group differences, while Cox regression models estimated hazard ratios (HRs) with 95% CIs to determine the impact of predictors on survival. Statistical analyses were conducted using R (v4.1.1), with $P < .05$ indicating significance.

Direct treatment costs for 2023 were calculated within Brazil's public health care framework (DataSUS), on the basis of the Authorization for High Complexity Procedures (AHCP). Costs for TNBC stages I-IV were determined by averaging systemic treatment expenses at Pérola Byington Hospital and presented in USD using the exchange rate of 1 USD = 5.61 Brazilian Real (July 3, 2024). Although treatment costs likely evolved over time, reimbursement rates remained unchanged during the study period, ensuring a consistent assessment of TNBC's economic impact.

RESULTS

We enrolled 1,266 patients with TNBC and 710 were included in the analysis. Figure 1 presents a flowchart that systematically

details the exclusion criteria and the final composition of the study population.

Characteristics of TNBC Patients

The characteristics of patients with TNBC at diagnosis were described on Table 1. The mean age at diagnosis was 52.5 years (standard deviation, 11.8). The ethnic distribution was predominantly Black (50.8%) followed by White patients (46.1%). The clinical staging at diagnosis showed that most patients were classified as stage III, accounting for 46.6%, followed by 42.1% at stage II. Chemotherapy regimens consisted of anthracyclines- and taxanes-based treatment, and regarding the treatment received, a total of 412 (58%) patients underwent neoadjuvant therapy, of whom 232 (54.6%) were treated with carboplatin and 96 (22.6%) achieved a pCR.

OS by Clinical Stage

Figure 2A presents Kaplan-Meier OS estimates for patients with TNBC receiving neoadjuvant treatment, stratified by clinical stage. Among the 13 stage I patients, one event occurred within the first 20 months (7.6% event rate). In stage II, 32 of 119 patients (26.9%) experienced events, while in stage III, 115 of 293 patients (39.2%) had events. A HR of 0.52 (95% CI, 0.32 to 0.82; $P < .001$) indicates a statistically significant OS difference between stage II and III groups. The survival graph only for stages II and III is presented in Appendix Figure A1.

TABLE 1. Characteristics of Triple-Negative Breast Cancer Patients at Diagnosis

Characteristic	Triple-Negative Patients (N = 710)
Age, years, mean	52.5 (11.8)
Ethnic origin, No. (%)	
White	327 (46.1)
Black	361 (50.8)
Asian	5 (0.70)
Undeclared	17 (2.39)
Clinical stage, No. (%)	
I	68 (9.58)
II	299 (42.1)
III	331 (46.6)
IV (de novo)	12 (1.69)
Treatment, No. (%[a])	
Neoadjuvant	412 (58.0)
Adjuvant	271 (38.2)
Neo and adjuvant	13 (1.83)
Palliative	12 (1.69)
Carboplatin-based treatment, No. (%[b])	
Yes	232 (54.6)
No	193 (45.4)
Neoadjuvant treatment, No. (%[b])	
pCR	96 (22.6)
No pCR	329 (77.4)

Abbreviation: pCR, complete pathologic response.
[a]There were two patients we could not use in the analysis because of inconsistences between the treatments.
[b]The percentage was calculated on the basis of the number of patients undergoing neoadjuvant treatment (n = 425).

OS by Neoadjuvant and Adjuvant Treatments

Figure 3 displays the OS analysis contrasting neoadjuvant and adjuvant treatments of patients with TNBC. The HR of 0.48 (95% CI, 0.34 to 0.69; $P < .001$) for all stages implies a 52% reduction in the risk of events for patients in the adjuvant treatment group compared with those in the neoadjuvant group. The HR stratified by stages on Appendix Figure A1 shows an HR of 0.26 (95% CI, 0.06 to 1.03) for stage I, and no difference between groups for stage II (HR, 0.62 [95% CI, 0.34 to 1.1]) and stage III (HR, 1.55 [95% CI, 0.9 to 2.68]).

OS by With or Without Complete Pathologic Response

Figure 4 presents the OS analysis for patients with TNBC who received neoadjuvant treatment, categorized by the presence or absence of pCR after treatment. The HR of 0.25 (95% CI, 0.13 to 0.48; $P < .001$) suggests that patients with pCR have a 75% reduction in the risk of events compared with those without pCR.

OS by Ethnic Origin

The Kaplan-Meier curves in Appendix Figure A1 contrast the OS probabilities between Black patients and those of other ethnicities diagnosed with TNBC and received neoadjuvant treatment. The HR was 0.73 (95% CI, 0.51 to 1.06), indicating no difference between the groups.

OS by With or Without Carboplatin-Based Neoadjuvant Treatment

The Kaplan-Meier curves in Appendix Figure A1 compare the OS probabilities between patients with TNBC treated with neoadjuvant carboplatin with those not treated with neoadjuvant carboplatin. The HR was 0.69 (95% CI, 0.47 to 1.00; $P < .001$), indicating no difference between groups.

Multivariate Analyses of OS

Multivariate analysis shows that achieving pCR is strongly associated with improved survival (HR, 0.21 [95% CI, 0.11 to 0.43]; $P < .001$). Stage II patients have better survival outcomes than stage III (HR, 0.53 [95% CI, 0.33 to 0.85]; $P = .009$), and Black patients show improved survival compared with non-Black patients (HR, 0.58 [95% CI, 0.40 to 0.86]; $P = .006$). However, carboplatin use does not significantly affect OS (HR, 0.96 [95% CI, 0.65 to 1.43]; $P = .857$). These data are shown in Figure 5.

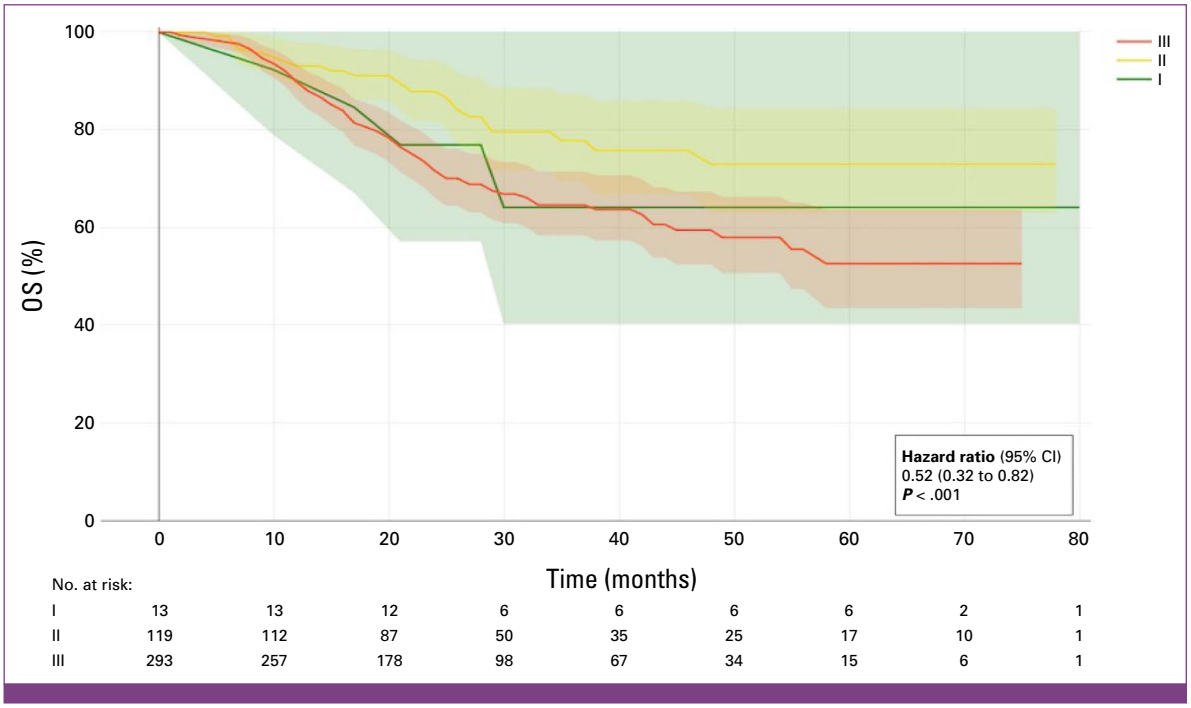

FIG 2. Kaplan-Meier OS estimates stratified by clinical stage for patients with TNBC. OS, overall survival; TNBC, triple-negative breast cancer.

Estimate the Cost for Each Stage in Patients With TNBC

Figure 6 displays the annual average cost per patient for systemic treating TNBC across different stages within the Brazilian public health care system from AHCP. There is a noted progressive increase in the average cost as the cancer stage becomes more advanced. The lowest costs are associated with stage I, at $101.87 USD monthly, and escalate to $314.77 USD for stage IV first-line treatment and $447.05 USD for second-line treatment.

The total annual cost for managing the systemic treatment of TNBC for stage I was $11,918.98 USD, accounting for 9.58% of patients. Stage II, encompassing 42.1% of cases,

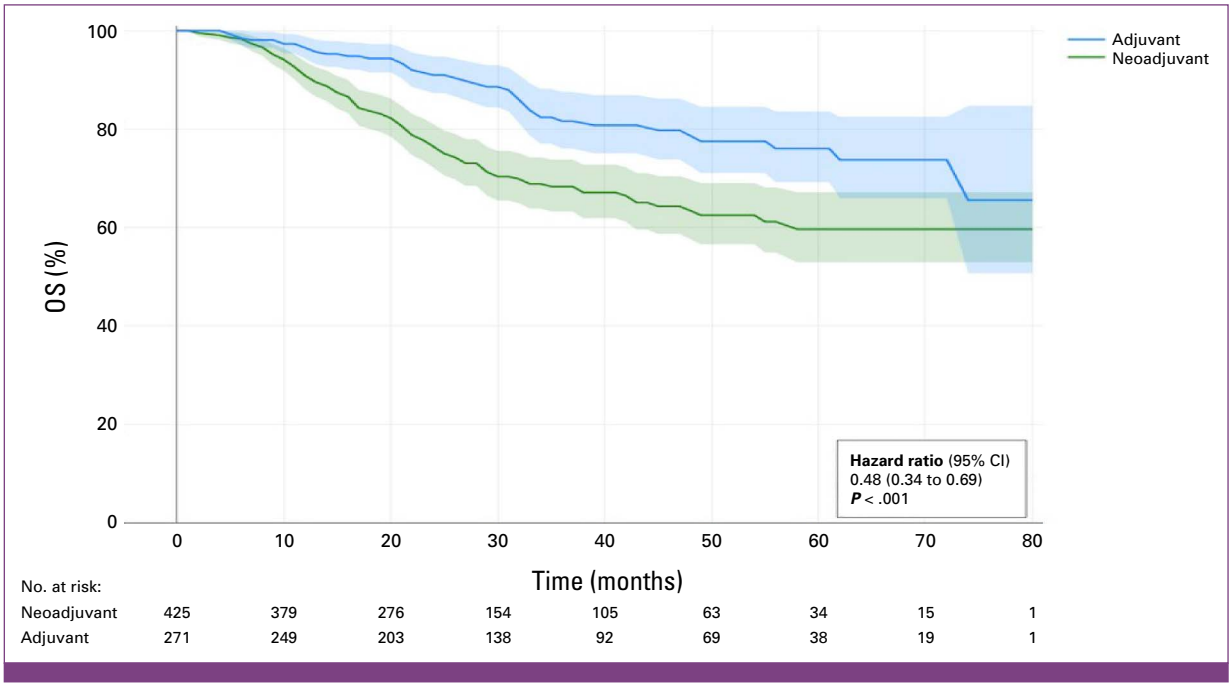

FIG 3. OS analysis by neoadjuvant and adjuvant treatments. OS, overall survival.

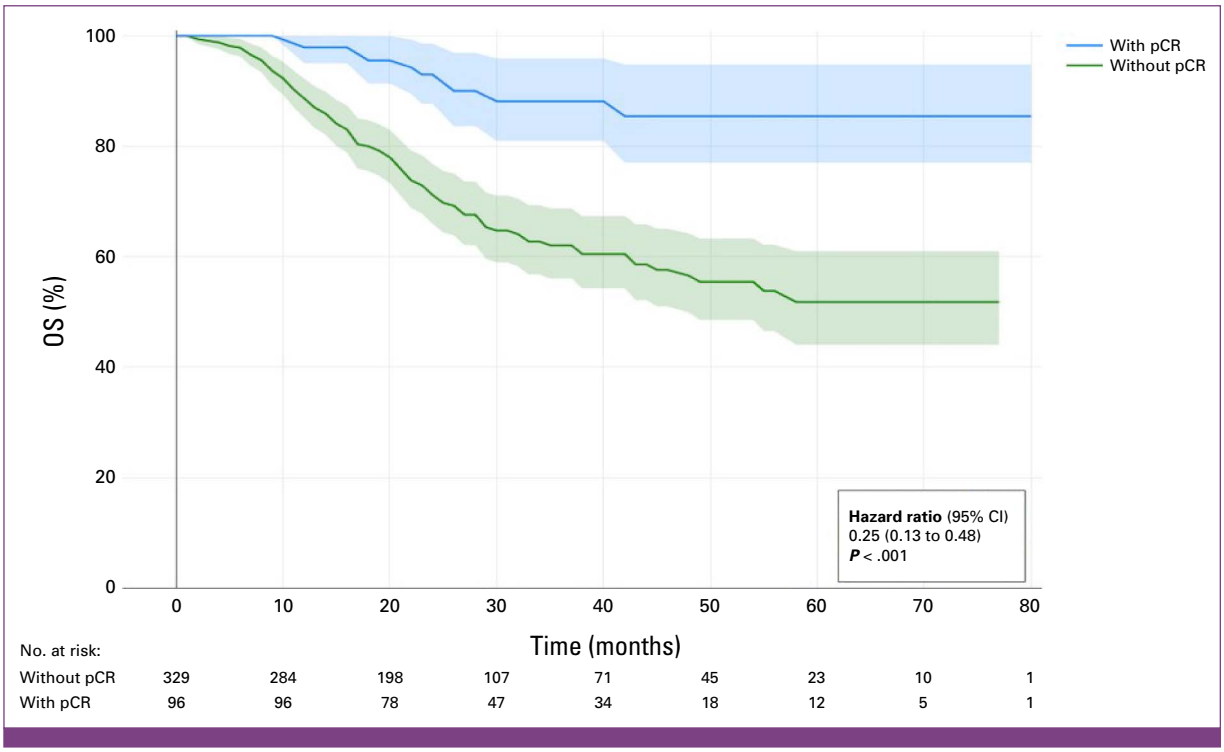

FIG 4. OS analysis by with and without pCR for patients with TNBC. OS, overall survival; pCR, complete pathologic response; TNBC, triple-negative breast cancer.

was responsible for annual costs of $45,632.80 USD. Stage III, the largest group at 46.6%, incurred the highest annual costs at $537,789.66 USD. Finally, stage IV, despite comprising only 1.69% of patients, resulted in extremely high annual costs, with first-line treatment at $335,547.24 USD and second-line treatment at $289,685.24 USD. The figure depicting the total annual cost for the management of systemic treatment of TNBC is presented in supplement figure e.

DISCUSSION

The Brazilian health care system comprises public and private sectors, with approximately 84% of the population relying on the public Unified Health System (UHS) for medical care. The UHS provides free access to a wide range of services, including cancer treatment, but faces challenges such as resource limitations, long wait times, and unequal access to advanced therapies. By contrast, the private sector, serving around 16% of the population, offers faster access to services and treatments, including options often unavailable in the public system.

In this RWD study encompassing 710 patients with TNBC treated within the UHS, we identified demographic and clinical characteristics at the time of diagnosis. The mean age was 52.5 years, with a predominantly Black ethnic

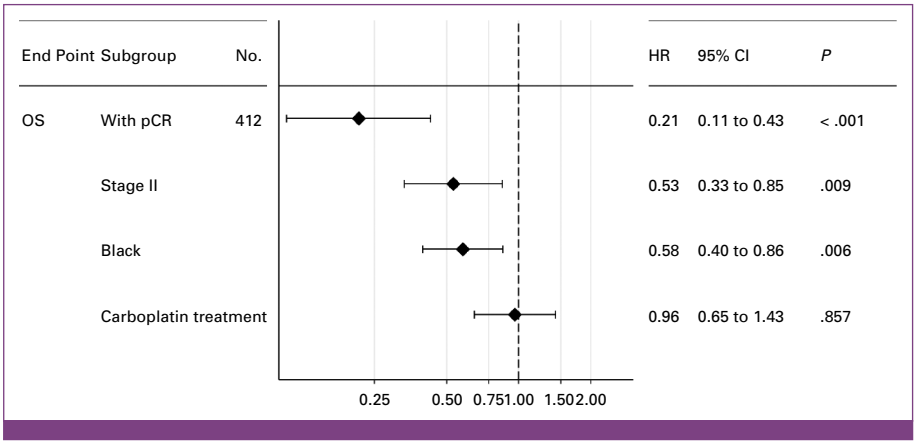

FIG 5. Multivariate analyses of OS. HR, hazard ratio; OS, overall survival; pCR, complete pathologic response.

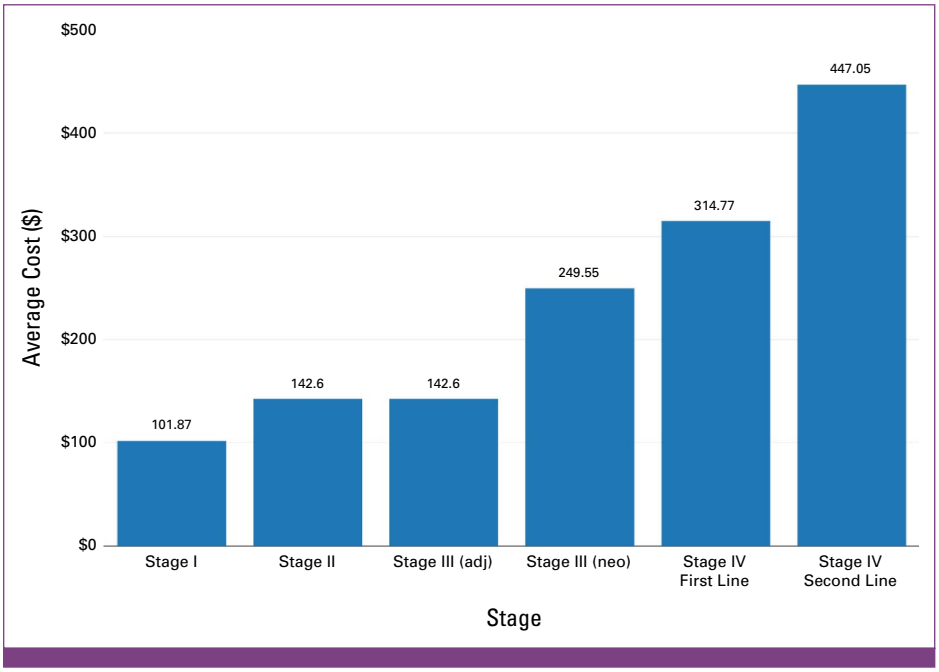

FIG 6. Distribution of systemic treatment costs by stage (average monthly cost per patient).

distribution. In this RWD, a declining gradient in OS was observed with advancing clinical stage, emphasizing the importance of early-stage intervention in TNBC, with stage II patients experiencing a reduced mortality risk compared with stage III. However, at diagnosis, the majority of patients with TNBC were classified in stage III, at worse prognosis; this is quite common in patients with limited access to screening and is especially true for young individuals, in whom the diagnosis tends to be clinical.[24] Notably, patients in the adjuvant treatment group exhibited a decrease in event risk compared with those receiving neoadjuvant therapy, but this can be explained because the neoadjuvant group had a higher proportion of stage III compared with those who received adjuvant treatment. The neoadjuvant treatment response has proven to be a pivotal factor, with patients who attained a pCR after neoadjuvant treatment showing reduction in the risk of events compared with those without pCR. Additionally, treatment with carboplatin and non-Black patient status showed no correlation with OS.

In our study, 22% of patients with TNBC achieved a pCR after neoadjuvant treatment, even with 54.6% of the patients receiving platin regimens. Two important hypotheses may explain these findings: the assistants included platin regimens only when the response with anthracyclines was not ideal and also the majority presence of stage III (46.6%). This is a common finding when the use of platins is not a routine and immunotherapy such as pembrolizumab is not available.[25] Because of the long period included (2010-2019), there was a significant treatment change in this period, and recently, carboplatin was included as standard of care in our hospital. Moreover, our results revealed that patients with TNBC who achieved a pCR experienced a 76% decrease in the risk of mortality compared with those who did not reach pCR, in line with findings from previous metanalyses.[26]

This outcome highlights the clinical importance of therapeutic strategies focused on maximizing response rates to achieve pCR as a key treatment goal. In Brazil's public health care system, TNBC treatment is limited to conventional chemotherapy, including anthracyclines, alkylating agents, taxanes, and fluoropyrimidines in neoadjuvant and adjuvant settings, with capecitabine, taxanes, and platins used for advanced disease.[3] To alter the reality of this context, it is necessary to prioritize early interventions and the incorporation of novel agents, particularly in resource-constrained settings such as Brazil's public health care system.[27]

The introduction of immunotherapy in high-income countries has transformed TNBC management.[14-16] Pembrolizumab, a PD-1 inhibitor, combined with chemotherapy as a neoadjuvant treatment, has shown significant potential in improving pCR rates, a key predictor of long-term survival. The I-SPY2 trial reported a pCR rate of 60% in the TNBC group treated with pembrolizumab and chemotherapy, compared with 22% in the control group, demonstrating substantial benefits.[28] Similarly, the KEYNOTE-522 trial found that pembrolizumab in combination with neoadjuvant chemotherapy improved event-free survival, suggesting both immediate and long-term advantages.[29] However, the safety profile requires attention, as pembrolizumab is associated with immune-related adverse events. Although trials indicate manageable toxicities, careful monitoring for immune-mediated effects is essential.[16] These findings highlight the potential for significant improvements

in survival outcomes, emphasizing the importance of integrating such innovative therapies into Brazil's public health care system to address disparities.[12,13]

Our sample consisted predominantly of Black patients (50.8%) and they have experienced better survival. In Brazil, we do have a heterogeneous population, and there is a big difference in African American population compared with Brazilian Black population and that can explain this finding. Typically, lower OS is found in Black population, and this might be hypothesized in Black patients because of disparities in health care access, potential for delayed diagnoses, and other social determinants of health. An analysis of US data from 1999 to 2015 showed that Black women with TNBC experienced worse 5-year and 10-year OS rates, particularly in areas with higher populations of Black residents, indicating the potential impact of regional demographics on health outcomes.[29] Brazil is characterized by its diverse ethnic composition, with significant proportions of the population identifying as White (47.7%), Black (9.1%), mixed-race (43.1%), Asian (1.1%), and Indigenous (0.4%), according to recent census data.[30]

This diversity has critical implications for health care outcomes, particularly regarding disparities in access. Black and Mixed-race populations in Brazil often face systemic inequities, such as delayed diagnoses, limited access to advanced treatments, and poorer health care infrastructure in regions with higher concentrations of these groups. To address these challenges, the UHS has implemented equity protocols, prioritizing access to specialized treatments for underserved populations and promoting educational initiatives for health care professionals. The improved outcomes observed among Black patients in our study may reflect the effectiveness of these equity measures in reducing disparities within Brazil's public health care system.[31] A prospective trial would be necessary to address these findings.

The annual average cost for systemic TNBC considering only chemotherapy treatment increases with disease progression: $110.97 USD for stage I and up to $486.97 USD for stage IV second-line therapy. The total cumulative cost ranges from $12,983.59 USD for stage I to $69,855.42 USD for stage IV treatment of TNBC. It is important to notice that our study exclusively includes the costs associated with chemotherapy, not incorporating costs related to other strategies such as ADCs, immunotherapy, and PARP inhibitors, as they are not available in the public setting.

Our study revealed that stage II patients had a 48% lower mortality risk compared with those at stage III, and patients receiving adjuvant treatment experienced a 52% reduction in mortality risk compared with those receiving neoadjuvant therapy. These findings underscore the importance of early intervention in TNBC management. Cost analysis showed that systemic treatment expenses were $101.87 USD per patient monthly for stage I, totaling $11,918.98 USD annually, and increased to $314.77 USD per patient for first-line stage IV treatment, accumulating to $625,232.48 USD for stage IV first- and second-line therapies. These results align with the analysis of Brazil's private health care system by Carlos Souto Maior Borba et al,[7] where the average PPPM for early and locally advanced TNBC was $7,351.72 USD, rising to $10,005.95 USD for metastatic TNBC.

The escalating costs of advanced-stage treatment highlight the dual benefits of early-stage intervention: improved survival rates and reduced financial burden. Later-stage treatments result in minimal survival gains but impose significant economic strain, illustrating inefficiencies in the health care system. To address these challenges, integrating clinical and economic strategies, including access to innovative agents, is critical in Brazil's resource-constrained public health care framework.[7]

This study's strength lies in its comprehensive analysis of RWD from 710 patients with TNBC treated within Brazil's public health care system. The rigorous retrospective analysis, conducted in line with ESMO's Reporting Oncology Real World Evidence guidelines, enhances the validity of our findings. Strict eligibility criteria, robust data management, and adherence to ethical standards further reinforce the study's reliability, supported by a decade of data from Pérola Byington Hospital.

However, limitations must be acknowledged. The exclusion of 0.7% of patients because of incomplete data, while necessary for quality assurance, may introduce selection bias. The retrospective design limits the ability to establish causality, and the cost analysis focused solely on systemic treatments, omitting hospitalizations, surgeries, and supportive care costs because of data constraints. Additionally, the single-center design may limit the generalizability of results across Brazil's diverse health care landscape.

Despite these challenges, this study represents a significant step forward in understanding TNBC in resource-limited settings. Future multicentric and prospective studies are needed to validate and extend these findings, providing critical real-world evidence to inform public health policies and optimize resource allocation, ultimately improving TNBC outcomes in low- and middle-income countries.

In conclusion, this study provides a comprehensive analysis of the clinical and epidemiologic profiles of patients with TNBC within Brazil's public health care system. A clear decline in OS was observed with advancing disease stages, highlighting the survival benefits of adjuvant therapy and achieving a complete pathologic response. Notably, Black individuals showed better survival outcomes compared with other ethnic groups, although no OS difference was found among patients receiving carboplatin as part of neoadjuvant therapy. Treatment costs increased significantly with advanced stages, emphasizing the importance of early intervention to improve outcomes and optimize resource allocation for TNBC management in Brazil.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

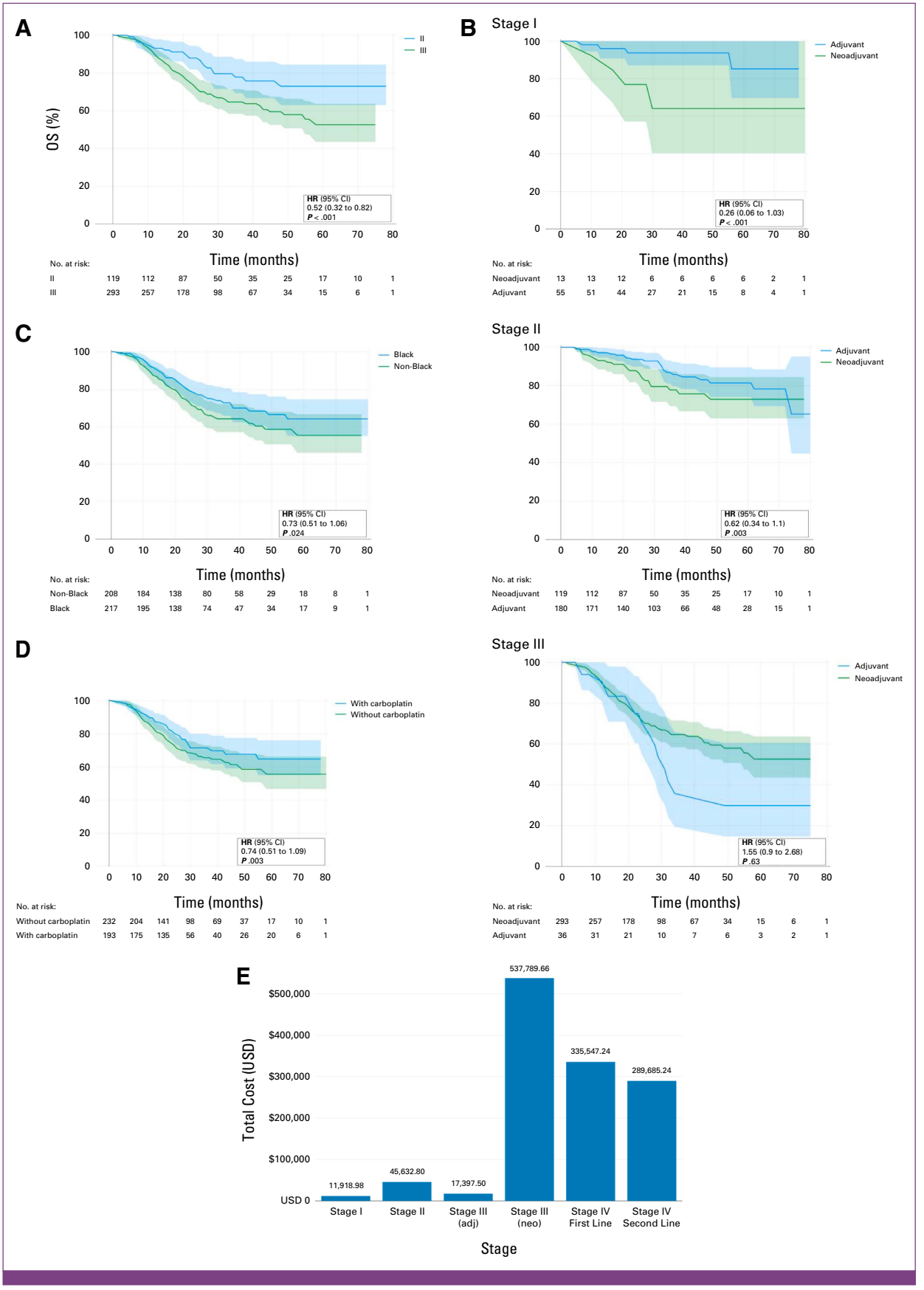

FIG A1. (Continued). **FIG A1.** (A) Kaplan-Meier OS estimates comparing II and III clinical stages for patients with TNBC. (B) OS analysis by neoadjuvant and adjuvant treatments for each stage. (C) OS analysis by ethnicity for patients with TNBC. (D) OS analysis by with and without carboplatin-based neoadjuvant treatment for patients with TNBC. The line on the graph denotes the median value, and the lighter shaded area surrounding it represents the 95% CI. (E) Distribution of systemic treatment costs by stage (accumulating annual cost). HR, hazard ratio; OS, overall survival; TNBC, triple-negative breast cancer; USD, US dollars.