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# Clinicopathological features, etiological factors and survival outcomes in breast cancer treated with neoadjuvant chemotherapy: a study from western Algeria

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## Abstract

Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer-related death among women. It is a biologically heterogeneous disease resulting from a multifactorial process. Neoadjuvant chemotherapy (NACT) has become a key treatment for patients with locally advanced or high-risk early-stage breast cancer, with its initiation guided by clinicopathological and etiological factors reflecting tumour aggressiveness and patient profile. This study aimed to describe the distribution of these factors among breast cancer patients treated with NACT in western Algeria, focusing on breast cancer subtypes and survival outcomes. We retrospectively analysed data from 327 breast cancer patients treated with NACT between January 2020 and December 2024. Data were collected from medical records and assessed among breast cancer subtypes using the chi-square test. Survival analysis was performed using the Kaplan–Meier method. In our cohort, most patients were aged 50 years or older (68.5%) and presented with a consultation delay exceeding 3 months after symptom onset. The Luminal B (LB) subtype was predominant (48.6%). High Ki-67 expression was observed in the majority of tumours, particularly among LB and triple-negative breast cancer (TNBC) subtypes. Histologically, Scarff–Bloom–Richardson grade II tumours were the most frequent in our cohort (64.5%). T2 tumours were prevalent, and nodal involvement was predominantly N1 stage. TNBC and human epidermal growth factor receptor 2-enriched subtypes showed poorer clinical outcomes, whereas hormone receptor (HR)-positive tumours were associated with better survival. These findings underline the predominance of breast cancer among middle-aged and older women and the value of Ki-67 as a marker of tumour aggressiveness. They also confirm the prognostic relevance of HR status and emphasise the importance of early detection and personalised follow-up, supported by molecular profiling and emerging biomarkers.

**Keywords:** *breast neoplasms*, *neoadjuvant therapy*, *biomarkers*, *risk factors*, *survival analysis*

Research

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## Background

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related mortality among women worldwide, accounting for an estimated 2.3 million new cases and 665,684 deaths in 2022 alone [1]. In Algeria, breast cancer is also a major contributor to female cancer deaths, accounting for 41.3% of all female malignancies, with 14,601 new cases diagnosed in 2022 [2].

Breast malignancies represent a biologically diverse group of diseases that might be observed at multiple levels, such as histopathological or molecular level [3–5]. This intrinsic heterogeneity influences not only the treatment decision but also the prognosis, underscoring the importance of tailored clinical management strategies [6,7].

In many studies, triple-negative breast cancer (TNBC) subtype is reported as having the worst prognosis, as patients do not benefit from endocrine or targeted therapies, leaving chemotherapy as the main systemic treatment option [8,9]. Furthermore, it was reported that Luminal B (LB) breast cancer shows substantially worse outcomes with a more aggressive phenotype compared to Luminal A (LA) breast cancer and has a distinct profile of response to hormone therapy and chemotherapy [10].

Besides, breast cancer emerges as a multifactorial disease, resulting from a complex interplay of genetic predispositions, hormonal influences, reproductive history, environmental exposures and lifestyle factors [11,12]. These etiological factors, along with tumour-specific characteristics such as grade, stage and receptor status, contribute to disease onset, progression and treatment response. Understanding the distribution of these factors among breast cancer patients is therefore essential for developing effective prevention strategies, optimising treatment choices and improving outcomes [6].

Over the past two decades, neoadjuvant chemotherapy (NACT) administered before surgical resection has emerged as a cornerstone in the management of patients with locally advanced or high-risk early-stage breast cancer [13]. Beyond contributing to tumour downstaging, improving operability and enabling breast-conserving surgery, NACT provides an *in vivo* evaluation of tumour sensitivity to therapy, offering crucial prognostic and predictive insights [14–16]. The decision to initiate NACT is often based on a combination of clinicopathological and etiological factors, which reflect both tumour aggressiveness and patient profile [17,18].

In this context, this study aims to describe the distribution of clinicopathological and etiological factors among breast cancer patients treated with NACT in western Algeria, with a specific focus on breast cancer subtypes. Analysing these distributions provides valuable insights into the profiles of individuals who undergo this therapeutic approach. In addition, the study examines metastasis free survival (MFS) and overall survival (OS) patterns, offering a deeper understanding of how tumour biology influences prognosis in patients receiving NACT.

## Methods

This retrospective descriptive study was carried out in the Department of Medical Oncology at the University Hospital Center of Oran (Algeria). The study included women diagnosed with breast cancer between January 2020 and December 2024.

### *Inclusion and exclusion criteria*

A total of 383 patients were initially identified from institutional medical records. Among these, 56 patients were excluded due to incomplete or missing data. Patients diagnosed with metastatic stage (M1) were also excluded. The remaining 327 patients met all inclusion criteria and were included in the study. Inclusion criteria were as follow: Residency in the western region of Algeria; Histological confirmation of breast cancer via core needle biopsy; Treatment with NACT before surgery; Known status of oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki-67.

### *NACT treatment*

All patients had received NACT according to their tumour subtype, stage at diagnosis, patient tolerance and the standard protocols followed in the institution. The most frequently used chemotherapy regimens included combinations of epirubicin plus cyclophosphamide (EC100) or doxorubicin plus cyclophosphamide (AC60). In some cases, taxane-based regimens were used, including docetaxel or paclitaxel, either

following anthracycline-based therapy or as monotherapy. The combination of carboplatin and taxane was occasionally administered. Trastuzumab was added for patients with HER2-positive tumours according to standard clinical indications.

### *Immunohistochemical profiling*

The expression of ER, PR, HER2, and Ki-67 proliferation index was determined by immunohistochemistry (IHC). HER2 status was confirmed by fluorescence *in situ* hybridisation in cases of equivocal IHC results (2+). ER and PR positivity were defined as nuclear staining in ≥1% of tumour cells. Ki-67 was considered high when the proliferation index exceeded 14%.

Breast carcinomas were classified as follows into four immunophenotypes acting as surrogates for the established molecular subtypes of breast cancer:

**LA:** ER+ and/or PR+, HER2- and a low Ki-67 proliferation index (≤14%).

**LB:** ER+ and/or PR+, HER2-, Ki-67 (>14%); ER+ and/or PR+, HER2+, any Ki-67.

**HER2-enriched:** ER-, PR-, HER2+.

**TNBC:** ER-, PR-, HER2-.

### *Data source*

The present study was conducted in compliance with the ethical principles of the Declaration of Helsinki, as revised in 2013. Data were extracted from hospital archives and electronic medical records. Given the observational and anonymised nature of the study, formal ethical approval was not required. No direct contact with patients occurred at any stage of the study. Throughout the study, confidentiality of patient information was strictly maintained.

### *Statistical analysis*

Statistical analyses were performed using the International Business Machines Corporation Statistical Package for the Social Sciences Statistics version 20.0. Descriptive statistics were used to analyse the distribution of clinicopathological and etiological features of the study population. Associations between these factors and breast cancer subtypes were evaluated using the chi-square test. Monte Carlo correction was applied to obtain accurate *p*-values in contingency tables with small expected frequencies. Survival analysis was performed using the Kaplan–Meier method. Differences between survival curves were assessed using the log-rank (Mantel-Cox) test. Median survival times and median follow-up were reported with their respective 95% confidence intervals (CI). OS was defined as the time from diagnosis to death from any cause or to the last follow-up for patients without an event. MFS was defined as the time from diagnosis to the occurrence of distant metastasis or to the last follow-up for patients without an event. Patients who died without developing distant metastasis were censored at the date of death. All statistical tests were two-sided at the 5% level of significance.

## Results

*Distribution of breast cancer patients and tumour characteristics among study population*

## Baseline patient characteristics and consultation patterns

A total of 327 female patients were included in this study. The descriptive analysis showed that most patients were aged 50 years and older at diagnosis (68.5%), with a median age of 55 years, and had a consultation delay exceeding 3 months following symptom onset (62.1%). A family history of breast cancer was reported in a subset of patients, though not predominantly (41.3%) (Table 1).

## Reproductive factors

Regarding reproductive factors, the majority of patients reported menarche occurring after the age of 12 (66.1%). While most patients were parous (67%), a large proportion had never breastfed (58.7%), and the majority were postmenopausal at diagnosis (63.9%). A history of oral contraceptive (OC) use was observed in 50.8% of cases (Table 1).

## Clinical and pathological tumour characteristics

In terms of tumour characteristics, the right breast was more frequently affected (48.3%), particularly in the upper outer quadrant (41.6%). Left breast was affected in 47.4% and bilateral in 4.3%. Histology showed that invasive carcinoma of no special type (NST) was the most prevalent (77.4%), with the majority of tumours classified as grade II (64.5%) followed by grade III (33.3%). Clinically, the T2 tumour stage was more frequent (46.8%), followed by the T4 stage (26.6%), and nodal involvement was predominantly N1 stage (62.7%). IHC showed that most tumours were positive for ER (65.4%) and PR (61.8%), while HER2-negative status was predominant (70.9%). A high Ki-67 proliferation index was observed in the majority of cases (59.9%) (Table 1), and LB subtype was the most represented among patients (48.6%) (Figure 1).



**Table 1. Baseline clinicopathological and etiological characteristics of the study population.**

| Characteristics | Patients *n* (%) |
|---|---|
| Age (years) | |
| <50 | 103 (31.5) |
| ≥50 | 224 (68.5) |
| Mean age | 55.90 ± 11.74 |
| Median | 55 |
| Presentation interval (months) | |
| ≤3 | 124 (37.9) |
| > 3 | 203 (62.1) |
| Family history of BC | |
| None | 192 (58.7) |
| Yes | 135 (41.3) |
| Menarche age (years) | |
| ≤12 | 111 (33.9) |
| >12 | 216 (66.1) |
| Parity | |
| Nulliparous | 108 (33) |
| Parous | 219 (67) |
| Breastfeeding | |
| No | 192 (58.7) |
| Yes | 135 (41.3) |
| Menopausal status | |
| Premenopausal | 118 (36.1) |
| Postmenopausal | 209 (63.9) |

*Continued*

**Table 1. Baseline clinicopathological and etiological characteristics of the study population.** *Continued*

| Characteristics | Patients *n* (%) |
|---|---|
| OC | |
| No | 161 (49.2) |
| Yes | 166 (50.8) |
| Affected breast | |
| Left | 155 (47.4) |
| Right | 158 (48.3) |
| Bilateral | 14 (4.3) |
| Tumour location | |
| Upper inner | 89 (27.2) |
| Upper outer | 136 (41.6) |
| Lower inner | 24 (7.3) |
| Lower outer | 22 (6.7) |
| Upper central | 22 (6.7) |
| Lower central | 20 (6.1) |
| Entire breast | 14 (4.3) |
| Histological type | |
| NST | 253 (77.4) |
| ILC | 52(15.9) |
| Others | 22 (6.7) |
| SBR grade | |
| Grade I | 7 (2.1) |
| Grade II | 211 (64.5) |
| Grade III | 109 (33.3) |
| Clinical tumour stage | |
| T1 | 13 (9.5) |
| T2 | 146 (46.8) |
| T3 | 60 (17.1) |
| T4 | 108 (26.6) |
| Clinical nodal stage | |
| N0 | 14 (4.3) |
| N1 | 205 (62.7) |
| N2 | 90 (27.5) |
| N3 | 18 (5.5) |
| ER IHC status | |
| ER- | 113 (34.6) |
| ER+ | 214 (65.4) |

*Continued*

**Table 1. Baseline clinicopathological and etiological characteristics of the study population.** *Continued*

| Characteristics | Patients *n* (%) |
|---|---|
| PR IHC status | |
| PR- | 125 (38.2) |
| PR+ | 202 (61.8) |
| HER2 IHC status | |
| HER2- | 232 (70.9) |
| HER2+ | 95 (29.1) |
| Ki67 IHC status | |
| Low | 131 (40.1) |
| High | 196 (59.9) |

This table summarises the baseline demographic, clinical, pathological and etiological features of patients included in the study, including age, tumour grade, breast cancer subtype, hormone receptor status, HER2 status, Ki-67 proliferation index and risk factors
Abbreviations: BC= Breast Cancer; ER= Oestrogen Receptor; HER2 = Human Epidermal growth factor Receptor 2; ILC = Invasive Lobular Carcinoma; NST = Invasive Breast Carcinoma of No Special Type; PR = Progesterone Receptor, SBR = Scarff–Bloom–Richardson

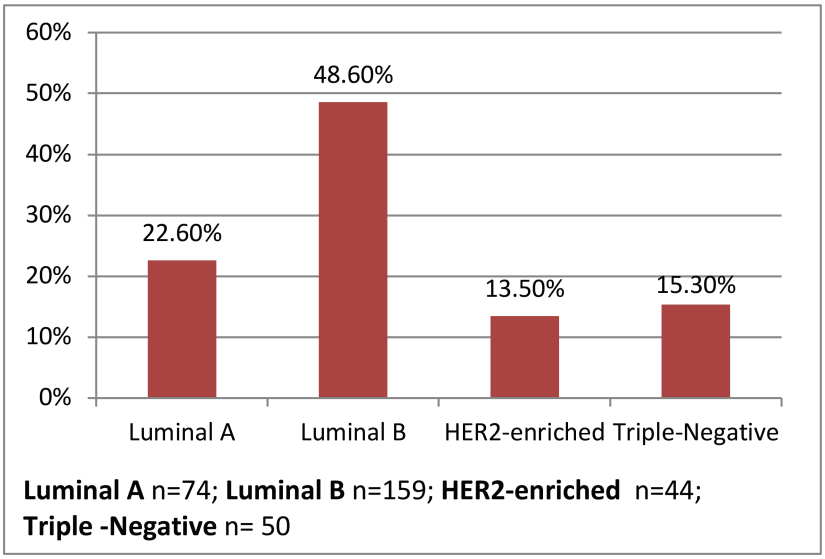


**Figure 1. Distribution of breast cancer subtypes in the study population. This figure illustrates the proportion of breast cancer subtypes in the study population, classified based on the immunohistochemical expression of ER, PR, HER2 and Ki-67.**

## *Distribution of breast cancer patients and tumour characteristics by breast cancer subtypes*

A comprehensive comparative analysis was conducted to evaluate the distribution of patients and tumours characteristics among each subtype of breast cancer.

## Baseline patient characteristics and consultation patterns

Patients aged 50 years and older represented the majority across all subtypes ($p$ = 0.05). Consultation delay exceeding 3 months was common in all groups, and family history of breast cancer was more frequently reported among LB and TNBC cases. However, no significant differences were observed between groups ($p$ > 0.05) (Table 2).

## Reproductive factors

Among all subtypes, most patients reported menarche after the age of 12, were parous, and postmenopausal at diagnosis. Breastfeeding was more frequently observed among patients with HER2-enriched tumours (54.5%). The use of OCs was more prevalent in the HER2-enriched (65.9%) and TNBC (52%) subtypes. Nevertheless, the distribution did not differ significantly between groups ($p$ > 0.05) (Table 2).

## Clinical and pathological tumour characteristics

Laterality differed significantly by subtype ($p$ <0.001) with left breast involvement being more common in LA and LB (47.3% and 54.1%, respectively), whereas right-sided tumours predominated in HER2-enriched and TNBC cases (72.7% and 56% respectively). Tumour localisation was most frequently detected in the upper outer quadrant across all subtypes. Invasive carcinoma of NST represented the most common histological type across all subtypes. In parallel, Scarff–Bloom–Richardson (SBR) grade II was the most frequently observed histological grade within each subgroup, except for the HER2-enriched group, in which grade III was significantly more frequent (50%) ($p$ = 0.046). Clinical tumour and nodal stages also varied significantly by subtype, but T2 and N1 were the most common stages observed across all of them ($p$ <0.05). IHC showed that while nearly all LA and LB subtypes were positive for both ER and PR, HER2 positivity was detected in 32.1% of LB cases ($p$ <0.001). A high Ki-67 index expression (>14%) was mostly observed in LB (90.6%) and TNBC subtypes (72%) ($p$ <0.001) (Table 2).



**Table 2. Distribution of clinicopathological and etiological characteristics among breast cancer subtypes.**

| Characteristics | LA<br>*N* = 74 | LB<br>*N* = 159 | HER2-enriched<br>*N* = 44 | TNBC<br>*N* = 50 | *p*-value |
|---|---|---|---|---|---|
| Age (years) | | | | | **0.050** |
| <50 | 29 (39.2) | 40 (25.2) | 19 (43.2) | 15 (30) | |
| ≥50 | 45 (60.8) | 119 (74.8) | 25 (56.8) | 35 (70) | |
| Mean age | 56.03 ± 12.05 | 55.84 ± 12.09 | 56.07 ± 11.22 | 56.16 ± 10.88 | |
| Median | 55.50 | 54 | 57 | 54.50 | |
| Presentation interval (months) | | | | | 0.817 |
| ≤3 | 26 (35.1) | 63 (39.6) | 18 (40.9) | 17 (34) | |
| > 3 | 48 (64.9) | 96 (60.4) | 26 (59.1) | 33 (66) | |

*Continued*

**Table 2. Distribution of clinicopathological and etiological characteristics among breast cancer subtypes.** *Continued*

| Characteristics | LA *N* = 74 | LB *N* = 159 | HER2-enriched *N* = 44 | TNBC *N* = 50 | *p*-value |
|---|---|---|---|---|---|
| Family history of BC | | | | | |
| None | 48 (35.1) | 94 (59.1) | 21 (47.7) | 29 (58) | 0.338 |
| Yes | 26 (64.9) | 65 (40.9) | 23 (52.3) | 21 (42) | |
| Menarche age (years) | | | | | |
| ≤12 | 29 (39.2) | 45 (28.3) | 15 (34.1) | 22 (44) | 0.143 |
| >12 | 45 (60.8) | 114 (71.7) | 29 (65.9) | 28 (56) | |
| Parity | | | | | |
| Nulliparous | 22 (29.7) | 59 (37.1) | 10 (22.7) | 17 (34) | 0.297 |
| Parous | 52 (70.3) | 100 (62.9) | 34 (77.3) | 33 (66) | |
| Breastfeeding | | | | | |
| No | 43 (58.1) | 99 (62.3) | 20 (45.5) | 30 (60) | 0.255 |
| Yes | 31 (41.9) | 60 (37.7) | 24 (54.5) | 20 (40) | |
| Menopausal status | | | | | |
| Premenopausal | 24 (32.4) | 59 (37.1) | 16 (36.4) | 19 (38) | 0.901 |
| Postmenopausal | 50 (67.6) | 100 (62.9) | 28 (63.6) | 31 (62) | |
| OCs | | | | | |
| No | 37 (50) | 85 (53.5) | 15 (34.1) | 24 (48) | 0.156 |
| Yes | 37 (50) | 74 (46.5) | 29 (65.9) | 26 (52) | |
| Affected breast | | | | | |
| Left | 35 (47.3) | 86 (54.1) | 12 (27.3) | 22 (44) | **<0.001** |
| Right | 31 (41.9) | 67 (42.1) | 32 (72.7) | 28 (56) | |
| Bilateral | 8 (10.8) | 6 (3.8) | 0 (0) | 0 (0) | |
| Tumour location | | | | | |
| Upper inner | 19 (25.7) | 43 (27) | 11 (25) | 16 (32) | |
| Upper outer | 22 (29.7) | 70 (44) | 24 (54.5) | 20 (40) | |
| Lower inner | 7 (9.5) | 9 (5.7) | 3 (6.8) | 5 (10) | |
| Lower outer | 9 (12.2) | 10 (6.3) | 2 (4.5) | 1 (2) | 0.117 |
| Upper central | 5 (6.8) | 15 (9.4) | 0 (0) | 2 (4) | |
| Lower central | 8 (10.8) | 5 (3.1) | 4 (9.1) | 3 (6) | |
| Entire breast | 4 (5.4) | 7 (4.4) | 0 (0) | 3 (6) | |

**Table 2. Distribution of clinicopathological and etiological characteristics among breast cancer subtypes.** *Continued*

| Characteristics | LA<br>*N* = 74 | LB<br>*N* = 159 | HER2-enriched<br>*N* = 44 | TNBC<br>*N* = 50 | *p*-value |
|---|---|---|---|---|---|
| Histological type | | | | | |
| NST | 60 (81.1) | 137 (86.2) | 27 (61.4) | 29 (58) | **<0.001** |
| ILC | 8 (10.8) | 14 (8.8) | 13 (29.5) | 17 (34) | |
| Others | 6 (8.1) | 8 (5) | 4 (9.1) | 4 (8) | |
| SBR grade | | | | | |
| Grade I | 3 (4.1) | 3 (1.9) | 1 (2.3) | 0 (0) | **0.046** |
| Grade II | 51 (68.9) | 100 (62.9) | 21 (47.7) | 39 (78) | |
| Grade III | 20 (27) | 56 (35.2) | 22 (50) | 11 (22) | |
| Clinical tumour stage | | | | | |
| T1 | 4 (5.4) | 5 (3.1) | 4 (9.1) | 0 (0) | **0.001** |
| T2 | 30 (40.5) | 58 (36.5) | 26 (59.1) | 32 (64) | |
| T3 | 15 (20.3) | 40 (25.2) | 2 (4.5) | 3 (6) | |
| T4 | 25 (33.8) | 56 (35.2) | 12 (27.3) | 15 (30) | |
| Clinical nodal stage | | | | | |
| N0 | 0 (0) | 13 (8.2) | 1 (2.3) | 0 (0) | **0.017** |
| N1 | 43 (58.1) | 98 (61.6) | 26 (59.1) | 38 (76) | |
| N2 | 26 (35.1) | 42 (26.4) | 12 (27.3) | 10 (20) | |
| N3 | 5 (6.8) | 6 (3.8) | 5 (11.4) | 2 (4) | |
| ER status | | | | | |
| ER- | 3 (4.1) | 16 (10.1) | 44 (100) | 50 (100) | **<0.001** |
| ER+ | 71 (95.9) | 143 (89.1) | 0 (0) | 0 (0) | |
| PR status | | | | | |
| PR- | 10 (13.5) | 21 (13.2) | 44 (100) | 50 (100) | **<0.001** |
| PR+ | 64 (86.5) | 138 (86.8) | 0 (0) | 0 (0) | |
| HER2 status | | | | | |
| HER2- | 74 (100) | 108 (67.9) | 0 (0) | 50 (100) | **<0.001** |
| HER2+ | 0 (0) | 51 (32.1) | 44 (100) | 0 (0) | |
| Ki67 status | | | | | |
| Low | 74 (100) | 15 (9.4) | 28 (63.6) | 14 (28) | **<0.001** |
| High | 0 | 144 (90.6) | 16 (36.4) | 36 (72) | |

This table presents the distribution of key etiological and clinicopathological factors across different breast cancer subtypes
Abbreviations: BC= Breast Cancer; ER= Oestrogen Receptor; HER2 = Human Epidermal growth factor Receptor 2; ILC = Invasive Lobular Carcinoma; NST = Invasive Breast Carcinoma of No Special Type; PR = Progesterone Receptor, SBR = Scarff–Bloom–Richardson
Bold values indicate statistical significance ($p \leq 0.05$).

### *Survival analysis*

The median follow-up time was 27 months (95% CI: 25.36–28.64 months). At the end of the study, 25 (7.6%) patients had died, and up to 146 (44.6%) participants had distant disease progression.

## Survival patterns among the study population

Kaplan–Meier analysis illustrated the survival distributions over time in our cohort. The median MFS was 32 months (95% CI: 27.08–36.92) (Figure 2), whereas the median OS was not reached (Figure 3).

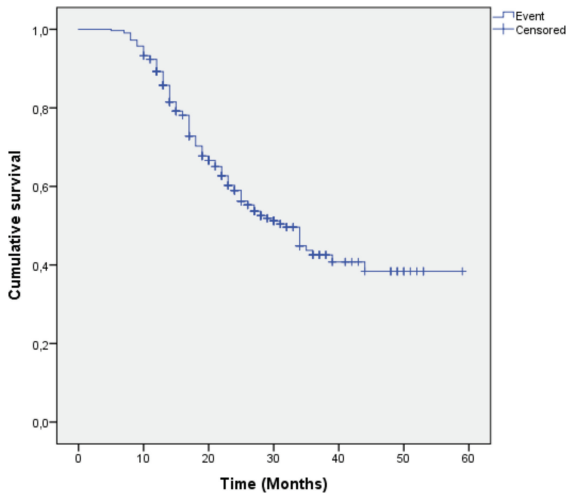


**Figure 2. MFS in the study population. This figure illustrates MFS in the entire study population. Survival analysis was performed using the Kaplan–Meier method. Censored observations are indicated by tick marks.**

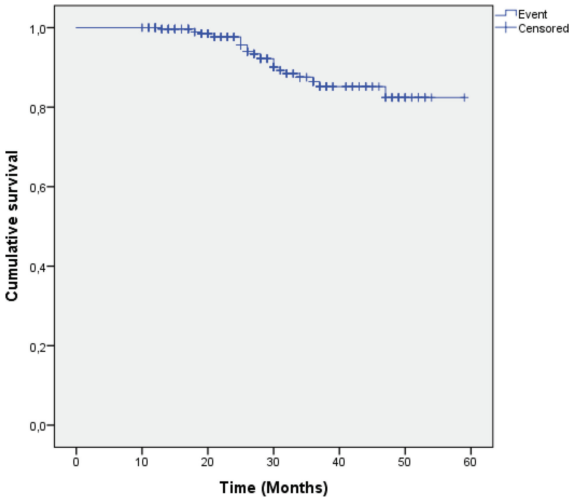


**Figure 3. OS in the study population. This figure illustrates OS in the entire study population. Survival analysis was performed using the Kaplan–Meier method. Censored observations are indicated by tick marks.**

## Survival patterns according to breast cancer subtypes

Five-year MFS and OS rates were analysed across breast cancer subtypes. Although no statistically significant difference was observed ($p$ = 0.464), LA tumours exhibited the most favourable MFS, while triple-negative and HER2-enriched subtypes tended to show poorer outcomes. LB cases demonstrated an intermediate survival pattern, less favourable than LA (Figure 4). OS exhibited a trend toward variation across breast cancer subtypes, approaching statistical significance ($p$ = 0.065), with triple-negative tumours exhibiting the poorest survival, followed by HER2-enriched tumours, whereas Luminal subtypes demonstrated the most favourable outcome (Figure 5).

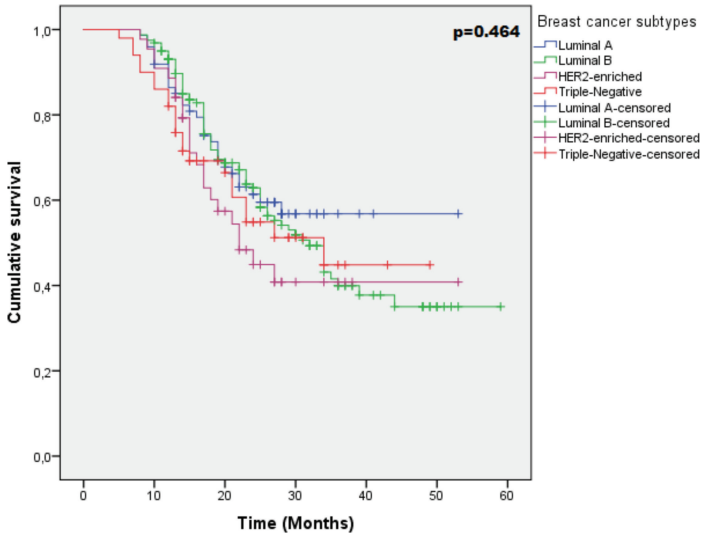


**Figure 4. MFS according to breast cancer subtypes. Kaplan–Meier survival curves showing MFS according to breast cancer subtypes. The difference between survival curves was assessed using the log-rank test. The variation in MFS across breast cancer subtypes was not statistically significant ($p$ = 0.464).**

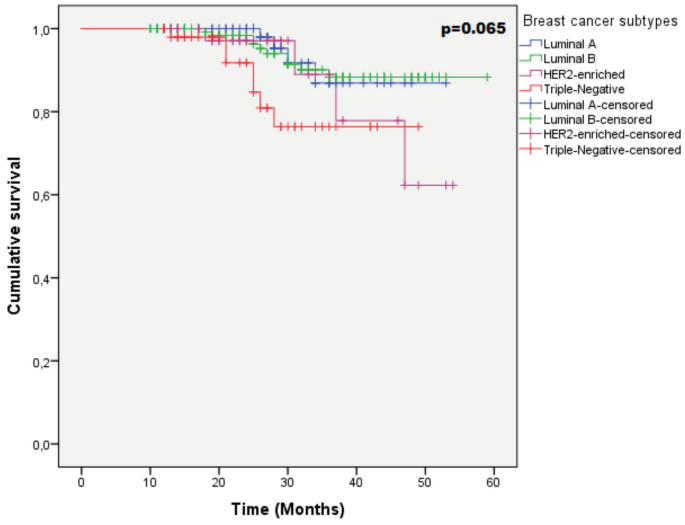


**Figure 5. OS according to breast cancer subtypes. Kaplan–Meier survival curves showing OS according to breast cancer subtypes. The difference between survival curves was assessed using the log-rank test. The variation in OS across breast cancer subtypes was not statistically significant ($p$ = 0.065).**

## Survival patterns according to LB subtype (HER2+ versus HER2–)

MFS analysis based on HER2 status within the LB subtype showed no statistically significant difference between the two subgroups ($p$ = 0.165). However, LB HER2-negative subtype exhibited an earlier and more pronounced decline in MFS than LB HER2-positive subtype (Figure 6). For OS, both LB HER2-positive and HER2-negative patients maintained high survival probabilities throughout the follow-up period, yet a modestly less favourable pattern was observed among LB HER2-positive patients, with no statistically significant difference between the curves ($p$ = 0.608) (Figure 7).

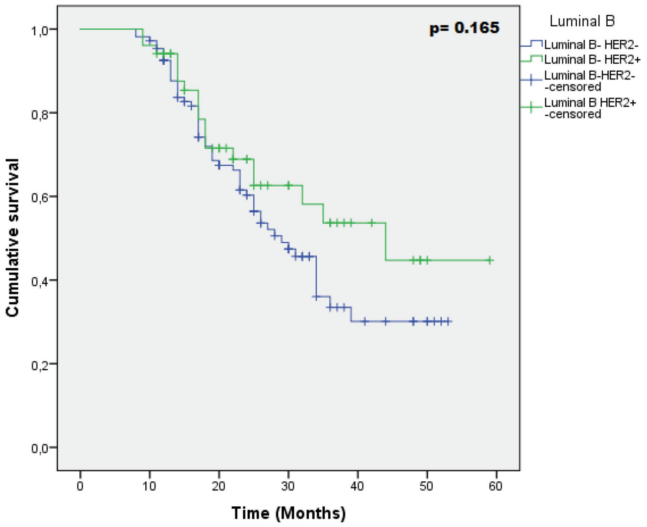


**Figure 6. MFS according to LB subtype. Kaplan–Meier survival curves showing MFS according to LB HER2-negative and LB HER2-positive subtypes. Differences between subtypes were assessed using the log-rank test. The variation in MFS across LB subtypes was not statistically significant ($p$ = 0.165).**

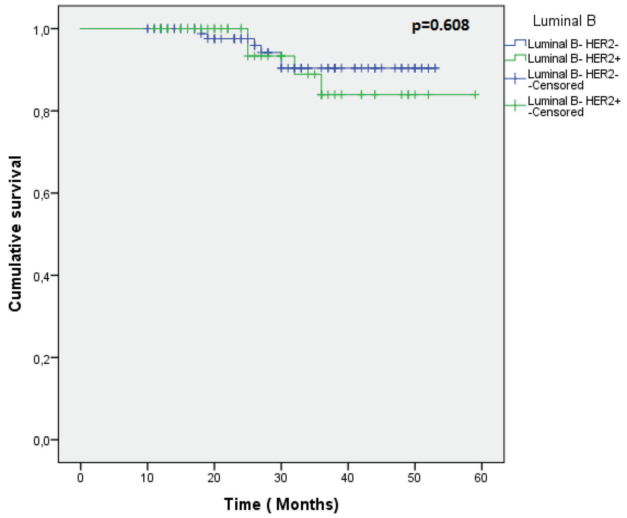


**Figure 7. OS according to LB subtype. Kaplan–Meier survival curves showing OS according to LB HER2-negative and LB HER2-positive subtypes. Differences between subtypes were assessed using the log-rank test. The variation in OS across LB subtypes was not statistically significant ($p$ = 0.608).**

## Survival patterns according to hormone receptors (HRs) status

Kaplan–Meier survival curves comparing HR status groups revealed a significant difference in OS with the HR-positive group showing a more favourable outcome ($p$ = 0.015) (Figure 8). HR-positive patients also showed better MFS compared to HR-negative patients; however, the difference was not statistically significant ($p$ = 0.156) (Figure 9).

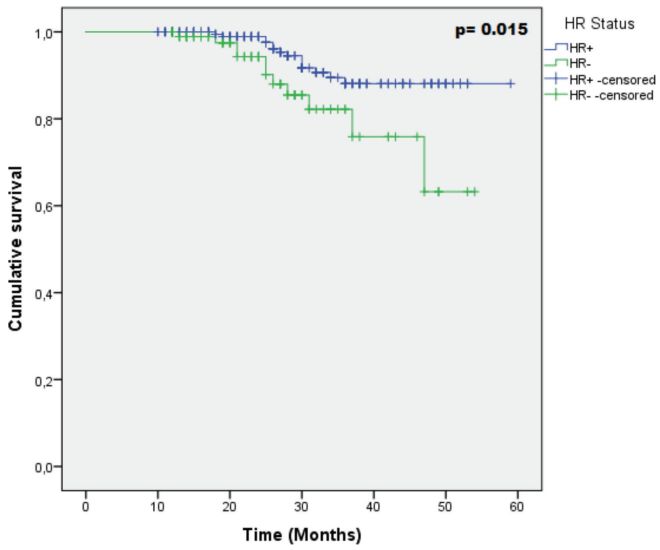


**Figure 8. OS according to HR status. Kaplan–Meier survival curves showing OS according to HR status (ER/PR). Differences between groups were assessed using the log-rank test. The variation in OS across the groups was statistically significant (p = 0.015).**

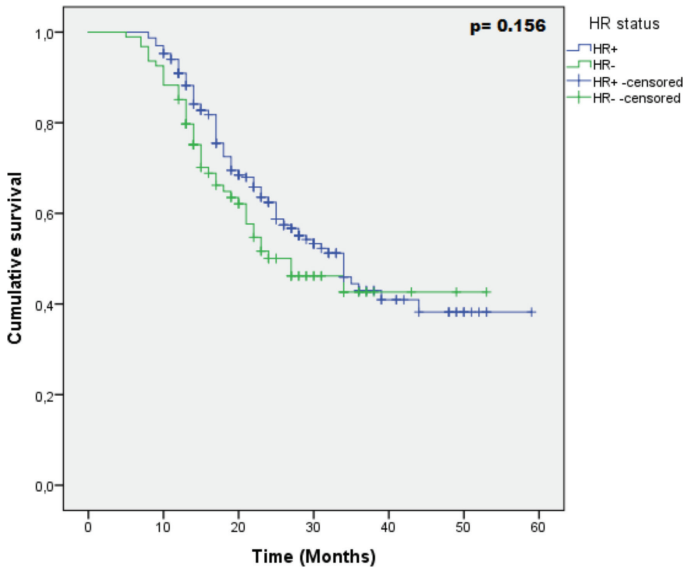


**Figure 9. MFS according to HR status. Kaplan–Meier survival curves showing MFS according to HR status (ER/PR). Differences between groups were assessed using the log-rank test. The variation in MFS across the groups was not statistically significant (p = 0.156).**

## Discussion

This study analyses the clinicopathological, etiological and molecular characteristics of breast cancer in patients treated with NACT in western Algeria, with particular emphasis on their distribution among breast cancer subtypes. It also explores their association with MFS and OS, shedding light on the prognostic impact of tumour biology among these patients.

The median age of patients in our cohort was 55 years, with a predominance of women aged 50 years and older (68.5%), indicating that breast cancer is more frequent among individuals in the sixth decade of life in our study population. While these data differ from some NACT-treated series that reported a predominance of younger patients [19, 20], they align with other studies describing similar age distribution. For instance, in a large cohort of 487 patients, the median age was 52 years, with 57.9% of cases aged between 50 and 70 years [21]. These findings suggest that, in certain settings, NACT is increasingly administered in older populations.

A key finding in our study was the substantial delay in consultation, with nearly two-thirds (62.1%) of patients seeking medical assistance more than 3 months after noticing breast changes. This delay, observed across all subtypes, may be attributed to limited awareness and barriers to early detection, frequently noticed in low- and middle-income countries, including limited access to healthcare facilities, cultural taboos and socioeconomic constraints [22]. Such delay serves as a major driver for the clinical severity of the disease and may partly explain the advanced disease characteristics prevalent in our cohort, characterised by larger tumour size and higher rates of nodal involvement at presentation. Similar trends have been reported in several African studies. For instance, Salih *et al* [23] found that only one quarter of patients sought medical attention within the first 3 months following symptom onset. Likewise, a study conducted in Uganda reported that 89% of women presented with a delay of more than 3 months [24]. Our observations are also consistent with the conclusions of previous reports identifying consultation delays as a major contributor to advanced-stage breast cancer diagnosis [25, 26]. This underscores the need for targeted awareness strategies and earlier diagnostic pathways to reduce advanced-stage presentation that may limit the effectiveness of treatment strategies.

Reproductive characteristics, including parity and late menarche, were frequent (67% and 66.1%, respectively). Although traditionally considered protective [27–29], their predominance in our cohort may be explained by interactions with other risk factors, including genetic susceptibility, environmental exposures and lifestyle factors, which could attenuate or even offset their expected protective effect. Our findings are consistent with those from Turkish [30] and Vietnamese [31] studies, which described comparable reproductive patterns among breast cancer patients with a predominance of parous women, accounting for 86% and 92.6% of cases, respectively, and late menarche occurring among 71.5% and 95.2%, respectively. These findings suggest that traditional protective reproductive factors may not fully reflect individual risk profiles, highlighting the need for a comprehensive approach to multifactorial risk assessment.

Beyond intrinsic reproductive history, we found that OC use was more prevalent among patients with HER2-enriched and TNBC tumours in our study. These findings align with a case-control study by Bethea *et al* [32] in African American women, which reported prior use of OCs in more than half of TNBC cases (282/495). Moreover, meta-analytic evidence shows a significant association between OC use and TNBC [33], although the link with HER2-enriched tumours remains less clearly established. This raises the possibility that exogenous hormones may have differential effects on the development of specific breast cancer subtypes. Consequently, further research, incorporating the duration and timing of exposure, is required to better understand the underlying biological mechanisms and their role in tumour heterogeneity and aggressive clinical phenotypes, which may ultimately contribute to improved individualised risk assessment strategies.

We also observed significant associations between breast cancer subtypes and tumour characteristics. Laterality varied significantly by subtype, with left-sided tumours being more frequent in LA and LB, and right-sided tumour predominance observed in HER2-enriched and TNBC. The reasons for these differences remain unclear at this stage and warrant further investigation. Our findings differ from American and European studies, which reported aggressive subtypes occurring more frequently in the left breast [34, 35]. These discrepancies highlight that laterality-related patterns are not consistent across populations and may be influenced by ethnic variations or environmental factors.

The upper outer quadrant was the most common tumour location across all subtypes. Such predominance may reflect the higher concentration of breast glandular tissue in this region as previously reported [36]. Our finding is consistent with the pattern reported in most breast

cancer studies worldwide, which show a dominance of the upper outer quadrant [37–39]. This implies that this area should remain a primary focus during imaging assessment and clinical examination due to its higher probability of harbouring malignant lesions.

In terms of clinical staging, T2 and N1 stages were the most frequently observed in the present study (46.8% and 62.7% respectively), reflecting a predominance of tumours with intermediate tumour size and early nodal involvement at diagnosis. This pattern may be influenced by the delayed presentation noted in a large proportion of patients. Our findings corroborate prior studies reporting a high prevalence of T2 and N1 stages in large NACT-treated cohorts [40, 41]. For instance, a retrospective study conducted by Cheun *et al* [42] in neoadjuvant settings showed that T2 and N1 stages were predominant, representing 70.2% and 43.7%, respectively. Clinically, this suggests that patients eligible for NACT are frequently diagnosed within this intermediate stage range that remains a critical period for tumour downstaging and improvement of surgical eligibility.

Histopathological examination revealed that invasive carcinoma of NST was predominant across all subtypes, in line with its well-established global predominance in breast cancer studies [20, 43]. However, the proportion of invasive lobular carcinoma (ILC), accounting for 15.9% of cases, was higher in our cohort than that reported in other NACT-treated series, such as those by Yilmaz and Cavdar [44] (7.5%) and Ghezzawi *et al* [45] (5.9%). This relative enrichment of ILC is particularly relevant to our earlier findings regarding age and stage, as this histological type is known to occur more frequently in older women and to be associated with a more insidious clinical presentation, often characterised by diffuse growth patterns and subtle radiological features that can delay clinical detection [46, 47]. These characteristics may have contributed to the more advanced clinical stages observed in our study.

Our investigation also revealed that SBR grade II tumours were more common in our cohort, particularly in both Luminal subtypes and TNBC, whereas SBR grade III tumours were significantly more prevalent among HER2-enriched tumours, reflecting the predominance of intermediate and high grade tumours in NACT-treated cohorts, concordant with international studies reporting similar distribution [48, 49]. This highlights the aggressive nature of tumours selected for NACT.

Immunohistochemical profiling revealed that the majority of patients had a high Ki-67 index (59.9%), in line with previous studies conducted in neoadjuvant settings [50, 51]. This reflects the predominance of highly proliferative tumours as a common feature in this context and confirms the overall aggressive tumour profile within our population. This pattern was particularly pronounced in LB and TNBC, both subtypes known to exhibit higher proliferative activity and poorer prognosis. Similar findings have been reported by a Lebanese study [52]. Ultimately, a high Ki-67 predominance underscores a rapid proliferative drive, linking aggressive biology to a higher risk of disease progression, thereby supporting the indication for NACT.

This proliferative phenotype is further supported by the predominance of the LB subtype (48.6%) within our population. Interestingly, our distribution pattern differs from several NACT-treated cohorts [53, 54]. One of these studies was conducted in Indonesia and reported a predominance of HER2-enriched subtype (32.37%) [55]. This discrepancy may be explained by differences in patient selection, particularly the inclusion of locally advanced breast cancer cases, as well as variations in tumour biology and population characteristics. Such findings point toward the heterogeneity of breast cancer subtype distribution in NACT-treated populations.

The clinical consequences of these biological patterns are reflected in survival outcomes. Although OS differences across subtypes did not reach statistical significance ($p$ = 0.065) - possibly due to the short 27 months median follow-up - a notable trend was observed. TNBC showed the poorest OS, followed by HER2-enriched tumours, consistent with their aggressive biology. In contrast, Luminal subtypes were associated with the most favourable OS, in line with their HR positivity. This survival pattern is comparable with the one reported by Kim *et al* [56] and Hennigs *et al* [57]. These trends support the prognostic value of immunophenotypic classification and its relevance in predicting survival outcomes among breast cancer patients. This prognostic hierarchy is more clearly elucidated when focusing specifically on HR status, which emerged as the most significant indicator of outcome in our study. We found that HR-positive patients had markedly better outcomes, with a significantly prolonged OS compared to their HR-negative counterparts ($p$ = 0.015). This reflects both the less aggressive tumour biology and treatment efficacy of hormone-sensitive tumours, emphasising the prognostic advantage conferred by HR expression. Our results align with existing literature highlighting the key role of HR status, such as the work of Ran *et al* [58] reporting a significantly improved OS and DFS in HR-positive patients compared to HR-negative ones [58]. This reinforces the importance of HR status assessment in guiding prognosis and therapeutic decisions.

MFS in our study also showed non-significant but consistent trends across breast cancer subtypes with LA tumours demonstrating the most favourable outcome. This may be related to intrinsic biological variations between subtypes, including the different proliferative activity, which may contribute to varying metastatic potential. These observations are in line with previously reported data, such as a study conducted in a Chinese cohort with operable breast cancer, where LA subtype had significantly higher 5-year DFS compared to other subtypes [59]. These findings highlight the prognostic heterogeneity between breast cancer subtypes, supporting the need for closer monitoring to detect and manage early metastatic progression in high-risk subtypes.

The major limitation of our study was the limited sample size, especially regarding specific breast cancer subtypes and the incomplete detailed data regarding treatment responses. This reduced the ability to perform robust subgroup analyses and explore treatment response within each subtype. As a result, potential subtype-specific associations might have been missed, highlighting the necessity of larger cohorts stratified by breast cancer subtype and treatment response in future investigations. The single-centre design of the study may also limit the generalisability of our findings. Finally, the median follow-up duration for our cohort was relatively short (27 months).

## Conclusion

Taken together, our findings revealed a predominance of the LB subtype in this cohort and the poor outcome associated with TNBC and HER2-enriched subtypes, reinforcing the prognostic value of HR status in breast cancer. The frequent presentation at advanced stages highlights persistent delays in diagnosis, likely driven by sociocultural and healthcare access barriers, which continue to compromise survival outcomes. The strong expression of Ki-67 among the most aggressive subtypes underscores the role of proliferation markers in characterising tumour behaviour, particularly in NACT-treated patients. Breast cancer in this cohort appeared mainly as a disease of middle-aged and older women, with a potential greater role of non-hormonal mechanisms in tumour initiation and progression. These observations underscore the importance of early detection and timely intervention. Besides, the integration of molecular profiling, detailed pathological assessment and innovative biomarkers could enhance post-treatment surveillance by allowing earlier detection of molecular relapses and guiding personalised therapeutic strategies to improve patient outcomes.



## List of abbreviations

AC60, Adriamycin (doxorubicin 60 mg/m$^2$) and cyclophosphamide; BC, Breast cancer; CI, confidence intervals; DFS, Disease-free survival; EC100, Epirubicin (100 mg/m$^2$) and cyclophosphamide; ER, Oestrogen receptor; HER2, Human epidermal growth factor receptor 2; HR, Hormone receptor; IHC, Immunohistochemistry; ILC, invasive lobular carcinoma; MFS, Metastasis-free survival; NACT, Neoadjuvant chemotherapy; NST, Invasive breast carcinoma of no special type; OS, Overall survival; PR, Progesterone receptor; SBR, Scarff–Bloom–Richardson; TNBC, Triple-negative breast cancer, TNM, Tumour, node, metastasis.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

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## Disclosure statement

Artificial intelligence-assisted tools (*ChatGPT*, *OpenAI*) were used only to improve language clarity and grammatical correctness. The authors reviewed and take full responsibility for the content.

## Author contributions

OHA: Methodology, Investigation, Data curation, Formal analysis, Interpretation, Visualisation, Writing – original draft; AR, AB, BEH: Resources, Validation; NNB: Writing – review & editing; LAK: Conceptualisation, Methodology, Supervision, Writing – review & editing.

## Author approval

All authors have read and approved the final manuscript and agree to its submission.

## Trial registration

Not applicable.



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