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Prevalence and manifestations of HER2-low breast cancer in patients with unrespectable and/or metastatic disease progressing on anticancer therapy: a retrospective study in the GCC region

Abstract

Background: The traditional binary classification of human epidermal growth factor receptor 2 (HER2) status in breast cancer (BC) has been challenged by recognition of the HER2-low subtype and the clinical benefits of novel HER2-targeted agents, such as trastuzumab deruxtecan. This study aimed to describe the prevalence, clinical features, treatment patterns, and outcomes of HER2-low BC in the Gulf Cooperation Council (GCC) region to identify the current unmet need for more effective treatment for this disease subgroup.

Methods: A retrospective, observational study included 500 patients diagnosed with HER2-negative, unresectable, and/or metastatic BC (mBC) from January 1, 2018, to December 31, 2022. We analyzed data from medical records across the United Arab Emirates, the Kingdom of Saudi Arabia, Qatar, and Kuwait.

Results: Among the 500 patients enrolled, 332 (66.4%, 95% CI: 62.3%-70.5%) were identified as HER2-low BC patients. The mean age at diagnosis was 53.4 years. Most patients were postmenopausal (57.8%), had invasive ductal carcinoma (86.4%), and were estrogen receptor-positive (93.7%). A majority (73.3%) were diagnosed at stage IV, with bone (72.3%) and lung (41.9%) being the most common metastatic sites. Nearly all patients received first-line (1L) therapy, most commonly CDK4/6 inhibitors with hormonal therapies (51.4%) or chemotherapy (17.4%). Combination therapies were primarily used in the first, second, and third lines before switching to single-agent therapy. Treatment discontinuation due to progression ranged from 28.3% to 38.6% across lines; adverse events accounted for up to 13% of the cases. Nearly 47.7% of patients experienced disease progression, and 7.6% relapsed after 1L therapy. The median real-world progression-free survival (rwPFS) was 16.4 months for 1L and 6.8 months for second-line therapies.

Conclusion: HER2-low subtype constitutes a significant proportion of mBC cases in the GCC region. Despite the available therapies, rwPFS results highlighted the need for more effective treatment approaches to improve patient outcomes.

Keywords: breast neoplasms, neoplasm metastasis, receptor, erbB-2, trastuzumab deruxtecan

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Abbreviations: ADC, antibody-drug conjugate; AEs, adverse events; BC, breast cancer; DOT, duration of treatment; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; GCC, Gulf Cooperation Council; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; IQR, interquartile range; ISH, in situ hybridisation; KSA, Kingdom of Saudi Arabia; mBC, metastatic breast cancer; OS, overall survival; PFS, progression free survival; PR, progesterone receptor; Q1, first quartile; Q3, third quartile; rwPFS, real-world progression-free survival; SD, standard deviation; TFST, time to first subsequent treatment; TTD, time to treatment discontinuation; T-DXd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer; UAE, United Arab Emirates

Introduction

Breast cancer (BC) is the most common malignancy among women and remains a leading cause of cancer-related mortality. The global burden of BC is rising; it is projected that by 2050, there will be 3.2 million new cases, with 1.1 million BC-related deaths per year.[1] In the Gulf Cooperation Council (GCC) region, BC often presents with distinctive features and a more aggressive nature than Western populations. These features include an earlier age at onset, more advanced stages at presentation, and higher pathological grades.[2] According to the 2020 Globocan Database, BC incidence in GCC countries ranges from 28.8 to 58.5 per 100,000 population.[2] In 2022, BC accounted for 6,932 new cases (32.3% of all cancers) and 1,911 deaths (22.4%).[3] These statistics underscore the need to understand BC biology and optimize treatment strategies in the region.

Breast cancer is a heterogeneous disease driven by differences in receptor expression, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).[4,5] Current treatment strategies rely on these biomarkers to guide personalized therapy.[6] HER2 is a key prognostic and predictive biomarker, assessed by immunohistochemistry (IHC) and in situ hybridisation (ISH).[7,8] This testing traditionally classifies tumors as HER2-positive or HER2-negative. While HER2-targeted therapies have significantly improved outcomes in HER2-positive advanced BC,[6] only 15–20% of tumors meet the criteria for HER2 positivity.[9] Approximately half of patients classified as HER2-negative exhibit

low levels of HER2 expression, limiting their eligibility for targeted therapies and leaving standard hormone- or chemotherapy-based regimens as the primary options.[9,10]

The HER2-low BC has recently been defined as IHC 1+/2+ without ISH amplification.[11] This subtype comprises approximately half of all BC cases, creating an opportunity for the expanded use of HER2-targeted therapies.[9] Although HER2-low BC has emerged as a clinically relevant therapeutic category, its biological distinction from HER2-zero disease remains under investigation. Current evidence suggests that HER2-low BC is not a distinct molecular entity but rather part of a continuum of HER2 expression, with tumor biology largely driven by hormone receptor (HR) status. Compared with HER2-positive tumors, HER2-low tumors generally exhibit lower levels of stromal tumor-infiltrating lymphocytes and a less immune-active microenvironment, resembling HER2-zero disease. Nevertheless, HER2-low tumors have demonstrated responsiveness to antibody-drug conjugates (ADCs), highlighting their clinical relevance.[11–13]

The development of trastuzumab deruxtecan (T-DXd), a novel ADC, has challenged the historical requirement for HER2 overexpression.[14] T-DXd combines a humanised anti-HER2 antibody linked via a cleavable linker to a membrane-permeable topoisomerase I inhibitor payload, enabling cytotoxic activity in cancer cells and adjacent cells through a bystander effect.[15,16] Clinical trials have established the therapeutic potential of T-DXd. In the DESTINY-Breast03 trial, T-DXd significantly improved overall survival (OS) compared to trastuzumab emtansine in HER2-positive metastatic BC (mBC).[17] DESTINY-Breast04 trial extended these findings to patients with HER2-low unresectable and/or mBC, showing a clinically significant OS benefit in both HR-positive and HR-negative cohorts.[18] These findings represent a paradigm shift, offering a targeted therapy to patients previously categorized as HER2-negative, including triple-negative breast cancer (TNBC), which is associated with poor prognosis and limited therapeutic options.[19,20] Recent research further suggests that T-DXd has a manageable safety profile, with improved tolerability when used earlier in the treatment sequence.[21]

Despite these advances, real-world data from GCC cancer centers remain limited. HER2 status is typically recorded as HER2-positive or HER2-negative with no routine differentiation of the HER2-low subgroup. Consequently, information on the prevalence, clinical features, treatment patterns, and outcomes of HER2-low BC in the region is lacking. This knowledge gap has become increasingly important given the evolving therapeutic landscape and the potential implications for patient management.

To address this gap, we conducted a retrospective, non-interventional, multicenter study across four GCC countries (the United Arab Emirates (UAE), the Kingdom of Saudi Arabia (KSA), Qatar, and Kuwait). The study aimed to estimate the prevalence of HER2-low BC among patients with unresectable and/or mBC previously classified as HER2-negative and to describe their demographic and clinical characteristics, treatment patterns, and outcomes across different lines of therapy.

Material and methods

Study design and participants

This retrospective, observational cohort study retrieved data from the medical records of patients diagnosed with HER2-low unresectable and/or mBC between January 1, 2018, and December 31, 2022, across ten sites in four GCC countries: the UAE, KSA, Qatar, and Kuwait. This cohort was selected to reflect real-world clinical outcomes among patients with HER2-low mBC who had previously received systemic anticancer therapy, in line with emerging interest in this evolving subtype. The data capture phase lasted 6 months, from July to December 2024. The study was conducted following approval by the relevant ethics committees and regulatory authorities. The study was registered at ClinicalTrials.gov (NCT06125314).

A total of 500 patients with a confirmed diagnosis of HER2-negative unresectable and/or mBC, between January 1, 2018, and December 31, 2022, were included in the study. Of these, 332 patients were identified as having HER2-low BC and constituted the primary analysis dataset (Figure 1).

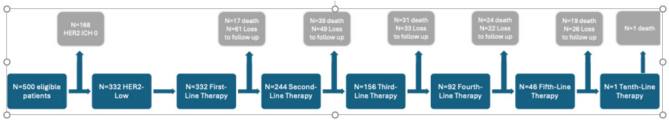

Figure 1 Study flowchart.

Eligible participants were women aged ≥18 years at diagnosis, with a histologically or cytologically confirmed diagnosis of unresectable and/or mBC within the specified period. Patients were also required to have at least 12 months of follow-up data at the participating site unless they died before completing 12 months. Patients had to be diagnosed with HER2-negative disease (defined as HER2 IHC 0, 1+, or 2+/ISH-), regardless of HR status. Patients must have been diagnosed with metastatic disease or experienced disease progression after receiving at least one prior systemic anticancer therapy in the metastatic setting (e.g., endocrine therapy (ET), chemotherapy, CDK4/6 inhibitors, targeted therapies other than anti-HER2, or immunotherapy).

In cases where HER2 IHC/ISH scoring was not clearly documented in the pathology report, patients were required to have archived fixed tissue HER2 IHC slides of acceptable quality to allow for HER2 re-evaluation.

Patients were ineligible for the study if they had a history of malignancies other than basal cell carcinoma of the skin and squamous cell carcinoma of the skin, or if they were HER2-positive with a documented HER2 status of IHC 2+/ISH+ or 3+, or HER2-amplified.

Data collection

Data were extracted from patients' medical records. For each patient, the follow-up period spanned from the date of HER2-negative unresectable and/or mBC diagnosis (de novo or progressed from early-stage BC) to the earliest of the following dates: death, loss to follow-up, or 31 December 2023. HER2 IHC scores were obtained from pathology reports at the time of diagnosis. If HER2 IHC scores were unavailable, HER2 status was reassessed using archived HER2 IHC slides.

Endpoints

The primary endpoint was the overall prevalence of HER2-low (IHC 1+, or 2+/ISH-) among unresectable and/or mBC patients who have been diagnosed or progressed after receiving at least one prior systemic anticancer therapy. These patients were identified as HER2-negative based on pathology reports with existing IHC HER2 scores, or, when scoring results were unavailable, by rescoring archived tissue specimens.

Secondary endpoints included baseline patient demographics and clinical characteristics, treatment patterns, and clinical outcomes of HER2-low BC patients across treatment lines, including time to treatment discontinuation (TTD), time to first subsequent treatment (TFST), duration of treatment (DOT), and real-world progression-free survival (rwPFS).

Citation: Bader SBJA, Altwairgi A, Altourah A, et al. Prevalence and manifestations of HER2-low breast cancer in patients with unrespectable and/or metastatic disease progressing on anticancer therapy: a retrospective study in the GCC region. *J Cancer Prev Curr Res*. 2026;17(4):128–137.
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Sample Size

A total of 500 patients with HER2-negative unresectable and/or mBC were enrolled in the study, among whom 332 were identified as having HER2-low disease. The sample size was primarily determined based on the objective of estimating prevalence. For prevalence estimation, a precision of ±5% is recommended for disease prevalence rates between 10% and 90%. The required sample size is largest when the expected prevalence is 50%. Under this assumption, at least 385 patients would be necessary to achieve a precision of ±5%.

Statistical analysis:

Data analysis was descriptive; numeric variables were summarized using means, standard deviations (SDs), medians, first quartile (Q1) and third quartile (Q3) and minimum and maximum values. Categorical variables were summarized by frequency distributions. Time-to-event data were summarized using the Kaplan-Meier method. Statistical analyses were performed using IBM SPSS (version 29, Armonk, NY, USA), and statistical significance was set at the 5% level.

Results

HER2 status and prevalence:

Among the HER2-negative patient population (N = 500), 332 patients were classified as HER2-low based on HER2 IHC/ISH test scores, corresponding to a prevalence of 66.4% (95% confidence interval [CI]: 62.3%-70.5%). Among the HER2-negative patients, 51.6% had HER2 IHC scores explicitly documented as HER2-low in the original pathology reports. In 19.8% of cases, the HER2 IHC score was not documented in the original pathology reports (Figure 2). The overall percentage of tissue samples available for testing was 99.2%, of which 76.6% were from the primary cancer site (Figure 3).

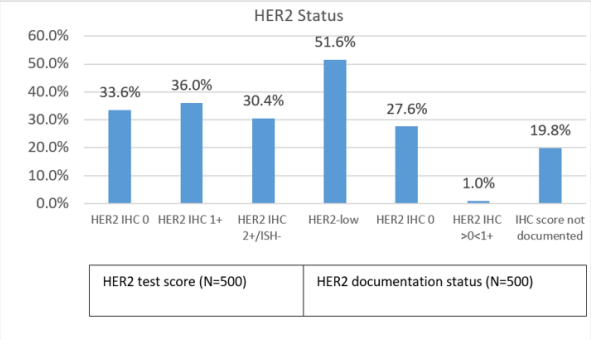

Figure 2 Distribution of HER2 status among patients with unresectable and/or mBC.

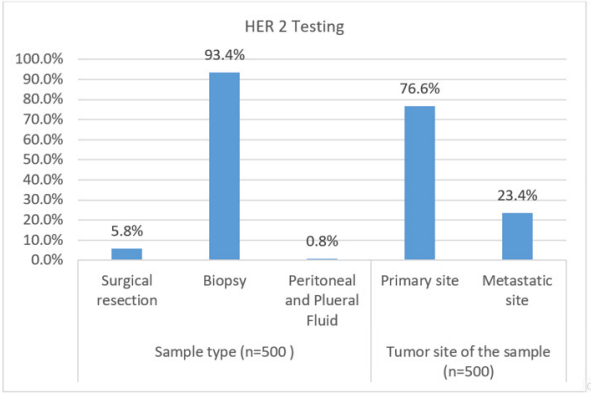

Figure 3 Specimen characteristics used for HER2 testing.

In cases where HER2 IHC scores were not explicitly documented in the original pathology reports, HER2 status was determined by reviewing archived tissue and available laboratory data, allowing classification of all patients.

Clinical and treatment characteristics of HER2-low BC patients

Baseline patient characteristics

Approximately 72.3% of patients were from the Middle East, with the majority born in the KSA (36.3%), the UAE (29.6%), and Qatar (29.0%). Half of the patients (50%) had an Eastern Cooperative Oncology Group (ECOG) performance status of zero, indicating that they were fully active. An additional 35.6% had an ECOG performance status of one, indicating some restrictions in physically strenuous activities. Only three patients were current smokers (1.0%), while 98.3% had never smoked. Most patients were postmenopausal (57.8%), and 37.6% were premenopausal (Table 1).

Table 1 Patients' demographics

Variable		Statistics n (%)
Race (n=332)	Middle Eastern	240 (72.3%)
	Asian	48 (14.5%)
	Other*	44 (13.3%)
Country of birth (n=331)	KSA	120 (36.3%)
	UAE	98 (29.6%)
	Qatar	96 (29.0%)
	Kuwait	5 (1.5%)
	Yemen	2 (0.6%)
	Sudan	2 (0.6%)
	Syria	2 (0.6%)
	Other**	6 (1.8%)
Smoking (n=288)	Current	3 (1.0%)
	Ex-smoker	2 (0.7%)
	Never smoker	283 (98.3%)
ECOG performance status Grade (n=298)	0	149 (50.0%)
	1	106 (35.6%)
	2	32 (10.7%)
	3	10 (3.4%)
	4	1 (0.3%)
Menopausal status (n=306)	Premenopausal	115 (37.6%)
	Perimenopausal	14 (4.6%)
	Postmenopausal	177 (57.8%)

*Other races included: African or African countries (n = 31), Arab/Arab countries outside Africa (n = 5), Asian countries (n = 4), and Western (n = 4). **One patient from each of Egypt, Indonesia, Morocco, Myanmar, the Philippines, and Pakistan.

Abbreviations: ECOG, eastern cooperative oncology group; KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates.

Among patients with available medical history data, slightly less than half (49.1%) had a history of comorbidities. The most common comorbidities were metabolic and nutritional disorders (64.1%) and vascular disorders (63.4%) (Table 2).

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Table 2 summary of patients' prior medical history, comorbidities and allergies

Variable		Statistics n (%)
Patients with Previous Medical History, Comorbidities or Allergies (n=289)	Yes	142 (49.1%)
	No	147 (50.9%)
Type of comorbidity (n=142)	Metabolism and nutrition disorders	91 (64.1%)
	Vascular disorders	90 (63.4%)
	Endocrine disorders	16 (11.3%)
	Cardiac disorders	11 (7.7%)
	Musculoskeletal and connective tissue disorders	10 (7%)
	Respiratory, thoracic, and mediastinal disorders	8 (5.6%)
	Renal and urinary disorders	6 (4.2%)
	Psychiatric disorders	4 (2.8%)
	Nervous system disorders	3 (2.1%)
	Surgical and medical procedures	3 (2.1%)
	Gastrointestinal disorders	3 (2.1%)
	Infections and infestations	2 (1.4%)
	Blood and lymphatic system disorders	2 (1.4%)
	Immune system disorders	1 (0.7%)
	Neoplasms benign, malignant, and unspecified*	1 (0.7%)
	Skin and subcutaneous tissue disorders	1 (0.7%)
	Congenital, familial, and genetic disorders	1 (0.7%)
	Hepatobiliary disorders	1 (0.7%)
	Injury, poisoning and procedural complications	1 (0.7%)
	Eye disorders	1 (0.7%)
	Investigations	1 (0.7%)

*Including cysts and polyps.

Clinical presentation at diagnosis

At the time of initial BC diagnosis, the median patient age was 52.1 years (interquartile range [IQR] 46–62). Most patients initially presented with grade II BC (63.1%) and stage IV disease (73.3%). Histologically, 86.4% had invasive ductal carcinoma (IDC), and 93.7% were ER-positive. The median tumor size was 4 cm, predominantly measured radiologically (60.5%). Among early-stage patients (n = 157), 68.2% received combination therapy, most commonly chemotherapy and CDK4/6 inhibitors (Table 3). The median age at diagnosis of metastatic disease was 56 years. The most frequently documented metastastic sites were bone (72.3%), lung (41.9%), liver (28.3%), and lymph nodes (18.1%) (Table 3).

Table 3 Clinical profile of HER2-low BC patients at diagnosis and metastatic presentation

Variable		Statistics
Age at initial BC diagnosis (years) (n=309)	Mean ± SD	53.4 ± 11.9
	Median (Q1-Q3)	52.1 (46–62)
	Min - Max	25.2–84.0
Grade at initial BC diagnosis (n=301)	I	18 (6%)
	II	190 (63.1%)
	III	93 (30.9%)
Stage at initial BC diagnosis (n=281)	I	7 (2.5%)
	II	27 (9.6%)
	III	41 (14.6%)
	IV	206 (73.3%)
Tumor size (cm) (n=279)	Mean ± SD	4.4 ± 2.6
	Median (Q1-Q3)	4 (2.5–5.9)
	Min - Max	0.5–12.5
Method of tumor size assessment (n=332)	Radiology	201 (60.5%)
	Pathology	131 (39.5%)
Histology at initial BC diagnosis (n=332)	IDC	287 (86.4%)
	ILC	33 (9.9%)
	DCIS	3 (0.9%)
	LCIS	1 (0.3%)
	Other*	8 (2.4%)
ER status (n=332)	Positive	311 (93.7%)
	Negative	21 (6.3%)
PR status (n=332)	Positive	291 (87.7%)

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Table 3 Continued...

	Negative	41 (12.3%)
Early BC Treatment (n=157)		
· Single treatment	Overall	50 (31.8%)
	Chemotherapies	34 (21.7%)
	Hormonal therapies	15 (9.6%)
	Others**	1 (0.6%)
· Combination therapy	Overall	107 (68.2%)
	Chemotherapies	65 (41.4%)
	CDK4/6 inhibitors	17 (10.8%)
	Hormonal therapies	14 (8.9%)
	Immunotherapies	1 (0.6%)
	Others***	10 (6.4%)
Age at metastatic diagnosis (years) (n=332)	Mean ± SD	55.2 ± 11.8
	Median (Q1-Q3)	56 (47–63)
	Min - Max	27–91
Site of metastases at presentation (n=332)	Bone	240 (72.3%)
	Lungs	139 (41.9%)
	Liver	94 (28.3%)
	Lymph nodes	60 (18.1%)
	Brain	14 (4.2%)
	Adrenal glands	5 (1.5%)
	Other sites†	31 (9.3%)

*Mixed ductal and lobular carcinoma (n = 2), invasive ductal carcinoma with lobular morphology (n = 1), Mucinous carcinoma (n = 1), Metastatic carcinoma of primary breast origin (n = 1), infiltrating mammary carcinoma of NST (n = 1), invasive mammary carcinoma and neuroendocrine tumors (n = 1), and unknown (n = 1).

**Radiation Therapy.

***Combination of CDK4/6 inhibitors and hormonal therapy (n = 8), combination of chemotherapy, radiotherapy, hormonal therapy, and surgery (n = 1), and surgery and radiotherapy (n = 1).

†Abdomen/GI/omental/peritoneal (n = 10), cervix/uterus/ovarian (n = 7), pleural (n = 7), skin (n = 3), spinal cord/spine (n = 2), pancreas (n = 1), liver (n = 1), bone marrow (n = 1), contralateral breast (n = 1), and chest (n = 1).

Abbreviations: BC, breast cancer; DCIS, ductal carcinoma in situ; ER, estrogen receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; PR, progesterone receptor; SD, standard deviation; Q1, first quartile; Q3, third quartile.

Treatment patterns across lines of therapy

Almost all HER2-low patients (99.7%) had received first-line therapy, with 73.5% receiving second-line therapy and 47% receiving third-line treatment. One patient received 10 lines of therapy. During first-line therapy, combination regimens were more prevalent than single-agent therapies; however, this changed with the third line, when most patients began receiving single-agent therapies. Detailed treatment regimens by line of therapy are summarized in Table 4.

Table 4 Treatment regimens and agents per line of therapy

Line of Therapy (n=332)	Regimen type	n (%)	Treatment Agents	n (%)*
First	Combination	252 (76.1%)	CDK4/6 inhibitors	165 (51.4%)
(n=331, 99.7%)	Single	70 (21.1%)	Hormonal therapies	165 (51.4%)
	Single/Combination	9 (2.7%)	Chemotherapies	56 (17.4%)
			Others	35 (10.9%)
			ET + CDK4/6 inhibitors	26 (8.1%)
			Targeted therapies	7 (2.2%)
			Immunotherapies	1 (0.3%)
Second	Combination	131 (53.7%)	Hormonal therapies	103 (42.2%)
(n=244, 73.5%)	Single	113 (46.3%)	Chemotherapies	89 (36.5%)
			CDK4/6 inhibitors	43 (17.6%)
			Targeted therapies	33 (13.5%)
			Others	15 (6.1%)
			ET + CDK4/6 inhibitors	8 (3.3%)
			Immunotherapies	3 (1.2%)

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Table 4 Continued...

Third	Combination	58 (37.2%)	Chemotherapies	88 (56.4%)
(n=156, 47%)	Single	98 (62.8%)	Hormonal therapies	38 (24.4%)
			Targeted therapies	22 (14.1%)
			Others	13 (8.3%)
			CDK4/6 inhibitors	9 (5.8%)
			Immunotherapies	4 (2.6%)
Fourth	Combination	23 (25%)	Chemotherapies	60 (65.2%)
(n=92, 27.7%)	Single	69 (75%)	Hormonal therapies	15 (16.3%)
			Targeted therapies	13 (14.1%)
			Others	6 (6.5%)
			Immunotherapies	3 (3.3%)
			CDK4/6 inhibitors	3 (3.3%)
Fifth	Combination	15 (33.3%)	Chemotherapies	28 (60.9%)
(n=46, 13.9%)	Single	30 (66.7%)	Targeted therapies	9 (19.6%)
	Single/Combination	1 (2.2%)	Hormonal therapies	7 (15.2%)
			Others	5 (10.9%)
			CDK4/6 inhibitors	2 (4.3%)
Sixth	Combination	3 (15%)	Chemotherapies	12 (60%)
(n=20, 6%)	Single	17 (85%)	Targeted therapies	3 (15%)
			Hormonal therapies	3 (15%)
			Immunotherapies	2 (10%)
			Others	1 (5%)
Seventh	Combination	1 (11.1%)	Chemotherapies	6 (66.7%)
(n=9, 2.7%)	Single	8 (88.9%)	Others	1 (11.1%)
			Targeted therapies	1 (11.1%)
			Hormonal therapies	1 (11.1%)
Eighth	Combination	1 (12.5%)	Chemotherapies	4 (66.7%)
(n=6, 1.8%)	Single	5 (62.5%)	Immunotherapies	1 (16.7%)
			Hormonal therapies	1 (16.7%)
Ninth	Combination	1 (50%)	Chemotherapies	2 (100%)
(n=2, o.6%)	Single	1 (50%)		
Tenth (n=1, 0.3%)	Combination	1 (100%)	Chemotherapies	1 (100%)

*Per each treatment line, percentages for treatment agents do not sum to 100% because patients may have received multiple therapies within the same line.

Abbreviations: ET, endocrine therapy

The proportion of patients who experienced disease relapse was 51.7% in the first-line therapy. Across subsequent lines, relapse rates ranged from 37.0% in the fifth line to 55.6% in the seventh line, based on the number of patients initiating each line of therapy, with progressively smaller patient numbers in later lines (Table 5).

Table 5 Relapse and treatment discontinuation per line of therapy

Line of therapy	Treatment completion	n (%)*	Treatment ongoing*	Disease relapse*
First (n=331)	Discontinuation due to disease progression	124 (38.6%)	30 (9.1%)	171 (51.7%)
	Discontinuation due to AE	22 (6.9%)		
	Completion	10 (3.1%)		
Second (n=244)	Discontinuation due to disease progression	85 (34.8%)	15 (6.1%)	110 (45.1%)
	Discontinuation due to AE	15 (6.1%)		
	Completion	3 (1.2%)		
Third (n=156)	Discontinuation due to disease progression	54 (34.6%)	10 (6.4%)	65 (41.7%)
	Discontinuation due to AE	10 (6.4%)		
	Completion	6 (3.8%)		
Fourth (n=92)	Discontinuation due to disease progression	30 (32.6%)	4 (4.3%)	43 (46.7%)
	Discontinuation due to AE	12 (13%)		
	Completion	2 (2.2%)		
Fifth (n=46)	Discontinuation due to disease progression	13 (28.3%)	2 (4.3%)	17 (37.0%)
	Discontinuation due to AE	5 (10.9%)		

Citation: Bader SBJA, Altwairgi A, Altourah A, et al. Prevalence and manifestations of HER2-low breast cancer in patients with unrespectable and/or metastatic disease progressing on anticancer therapy: a retrospective study in the GCC region. *J Cancer Prev Curr Res*. 2026;17(4):128–137.
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Table 5 Continued...

	Completion	1 (2.2%)		
Sixth (n=20)	Discontinuation due to disease progression	7 (35%)	0 (0%)	9 (45.0%)
	Completion	1 (5%)		
Seventh (n=9)	Discontinuation due to disease progression	6 (66.7%)	0 (0%)	5 (55.6%)
Eighth (n=6)	Discontinuation due to disease progression	2 (33.3%)	0 (0%)	3 (50.0%)
	Discontinuation due to AE	1 (16.7%)		
Nineth (n=2)	Discontinuation due to disease progression	1 (50%)	0 (0%)	1 (50.0%)
Tenth (n=1)	Discontinuation due to disease progression	1 (100%)	0 (0%)	0 (0%)

*The percentage is taken per number of patients in each line of therapy.

Abbreviations: AE, adverse event.

Regarding treatment completion and reasons for discontinuation, among patients receiving first-line therapy, 6.9% discontinued due to adverse events (AEs), a rate similar to those for second-line (6.1%) and third-line therapies (6.4%). Discontinuation rates due to AEs rose with fourth and fifth lines, reaching 13.0% and 10.9%, respectively. Additionally, 38.6% of first-line patients discontinued treatment due to disease progression, which aligns with rates of 34.8% and 34.6% for second- and third-line therapy patients, respectively. These rates remained relatively high in subsequent therapies (Table 5).

Clinical outcomes by line of treatment

Real-world progression-free survival

The median rwPFS for first-line therapy was 16.4 months (95% CI 14.4–18.3) (Figure 4). For second-line therapy, the median rwPFS was 6.8 months (95% CI 5.8–7.8) (Figure 5).

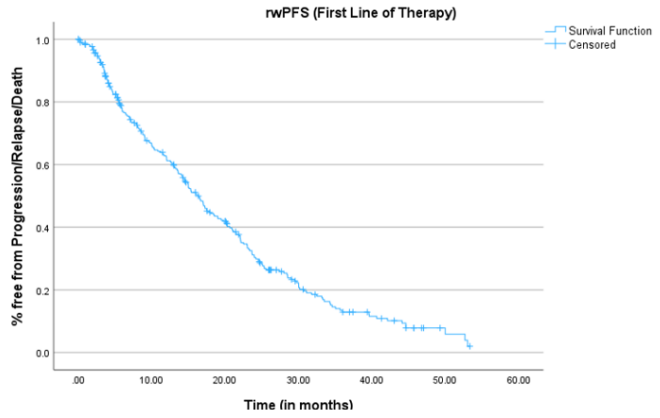

Figure 4 rwPFS in patients receiving first-line therapy.

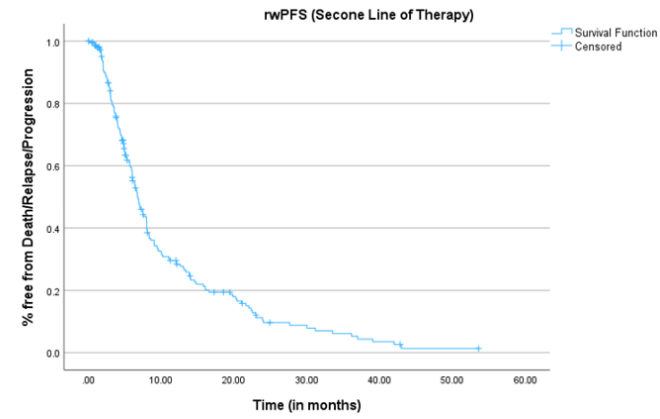

Figure 5 rwPFS in patients receiving second-line therapy.

Time to discontinuation

The median TTD on first-line therapy was 15.4 months (95% CI 13.6–17.1) (Figure 6). For second-line therapy, the median TTD was 6.7 months (95% CI 5.8–7.7) (Figure 7).

Treatment duration

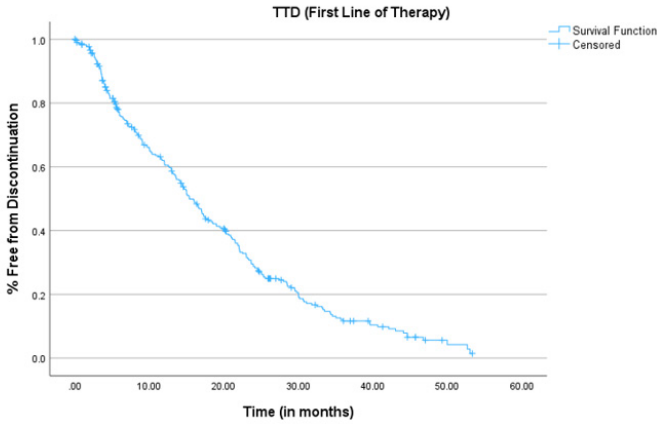

Figure 6 TTD in patients receiving first-line therapy.

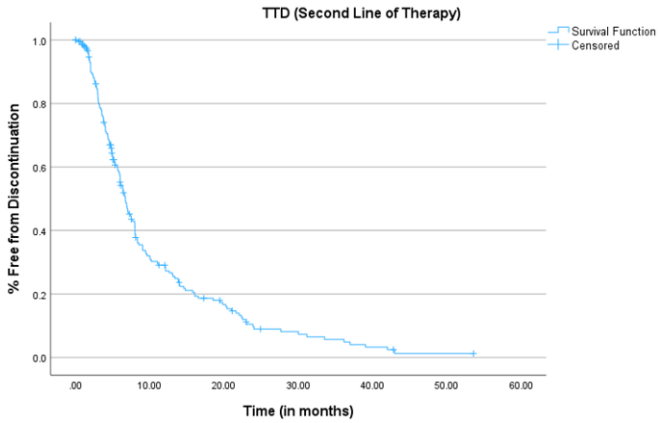

Figure 7 TTD in patients receiving second-line therapy.

The median TFST for patients on first-line therapy was 13.6 months (IQR: 5.7-22.1 months), while for those on second-line treatment, it was 6.5 months (IQR: 4.0-12.1 months). The median DoT for patients on first-line therapy was also 13.6 months (IQR: 5.4-23 months), whereas for second-line treatment, it was 5.8 months (IQR: 3.1-10.3 months) (Table 6).

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Table 6 TFST and DoT for first and second lines of treatment

Variable		Summary statistics	
TFST* (in months)	First Line of Therapy	Mean ± SD	15.4 ± 11.4
	(n=229)	Median (Q1-Q3)	13.6 (5.7–22.1)
		Min - Max	0.9–61.4
	Second Line of Therapy	Mean ± SD	9.3 ± 8.3
	(n=146)	Median(Q1-Q3)	6.5 (4.0–12.1)
		Min - Max	0.03–43.1
DoT (in months)	First Line of Therapy	Mean ± SD	16.0 ± 12.3
	(n=265)	Median (Q1-Q3)	13.6 (5.4–23.0)
		Min - Max	0.03–53.3
	Second Line of Therapy	Mean ± SD	8.9 ± 9.6
	(n=198)	Median (Q1-Q3)	5.8 (3.1–10.3)
		Min - Max	0.03–57

*Switching to the first subsequent therapy may have occurred for reasons other than disease progression, including adverse events, patient's preference, physician decision, or other unspecified reasons.

Discussion

This study examined the prevalence and clinical characteristics of HER2-low BC in patients with advanced and/or metastatic disease in four countries in the GCC region. Out of 500 patients, 332 were identified as HER2-low, representing 66.4% of the cohort. Most patients were postmenopausal with IDC, and a significant number presented with stage IV disease, with bone and lung as the most common metastatic sites. Treatment patterns revealed that many patients received combination therapies as their first- and second-line treatments, with a median rwPFS of 16.4 and 6.8 months, respectively, in addition to declining TTD, TFST, and DoT. Despite existing treatment options, our findings underscore the importance of recognizing HER2-low status to improve treatment outcomes.

In our cohort, HER2-low accounted for 66.4% of HER2-negative, unresectable and/or mBC cases. This prevalence aligns with that reported in a global multicenter study (67.2%),[22] and is notably higher than the 32% reported in five European countries[23] and Latin America[24] as well as the 41.7% reported in South Korea,[25] and 54.5% reported in China.[26] These differences may reflect diverse patient demographics, disease characteristics, and HER2 testing criteria, but overall reinforce that HER2-low disease represents a substantial and clinically relevant subgroup globally. In the GCC region, there is a notable lack of published data on the frequency of HER2-low expression. However, the TNBC population was previously investigated.[27,28] It is a challenging subgroup with historically limited treatment options and a poorer prognosis. Distinguishing HER2-low disease from true TNBC within HER2-negative populations is therefore essential, as it may identify patients who could benefit from emerging HER2-targeted therapies. This lack of regional evidence underscores the importance of our findings and their clinical implications.

Consistent with global patterns, our cohort was predominantly postmenopausal, with a median age at diagnosis exceeding 50 years, and most tumors were IDC and ER-positive disease.[29] Among patients with available data, 49.1% had at least one comorbidity, primarily metabolic and nutritional conditions (64.1%) and vascular disorders (63.4%). This is consistent with recent real-world findings in HR+/HER2-negative mBC patients, where 61.7% of patients had cardiovascular comorbidities, mainly hypertension, followed by hyperlipidemia and diabetes mellitus.[30] The median tumor size in our cohort was 4 cm (IQR: 2.5–5.9 cm), which closely matches SEER-based analyses of patients presenting with de novo mBC, where mean tumor sizes across age groups range from approximately 4.6 to 5.1 cm.[31] More than 70% of our patients were diagnosed at stage IV, indicating potential delays in detection or distinctive tumor characteristics in this population. Aligned with international data, bone was the most common metastatic site, affecting over 70% of patients, followed by lung and liver involvement.[32]

Data on prior treatments in the early BC setting show that most patients received combination therapy (68.2%), while the rest received single agents. Our analysis focused on treatment patterns and outcomes in the metastatic setting. Nearly all patients received first-line therapy, with 51.4% receiving CDK4/6 inhibitors in combination with hormonal therapies, per the NCCN and ESMO guidelines for HR+/HER2-negative mBC.[22,33]As disease progressed to subsequent lines, treatment patterns shifted toward increased use of chemotherapy, rising from 17.4% in first-line to over 65% by the eighth-line therapy, and up to 100% in the ninth and tenth lines of treatment. This highlights the limited durability of endocrine-based strategies in advanced disease and the reliance on cytotoxic regimens in later lines.[22,34] Targeted therapies were employed more frequently in later lines, and a small proportion of patients received immunotherapy. The marked decline in patient numbers beyond the fourth-line therapy highlights the aggressive nature of the disease and limited survival beyond multiple treatment lines.

Our data reveal that disease progression was the primary reason for treatment discontinuation across all lines, consistent with global reports.[35] Discontinuations due to adverse events, although lower overall, rose in later lines and may reflect the impact of cumulative toxicity. Furthermore, treatment completion rates were notably low, and a significant proportion of patients experienced disease relapse. These findings highlight the clinical challenge of maintaining disease control and tolerability across successive lines, reinforcing the unmet need for more durable, well-tolerated therapeutic strategies, particularly in the HER2-low subgroup.

Our study showed that clinical outcomes declined markedly with successive lines of therapy. The median rwPFS was 16.4 months in the first-line setting, dropping to 6.8 months in the second-line setting, and the median TTD fell from 15.4 to 6.7 months. Similar trends were observed across TFST and DoT, highlighting progressively shorter durations of disease control and therapy as patients moved through lines of treatment. This is consistent with real-world evidence demonstrating that palbociclib (CDK4/6 inhibitor) plus ET achieves

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approximately 19.3 months of rwPFS in the first line versus 13.9 months with ET alone.[36] The median PFS with first-line chemotherapy was 6.9 months, which decreased with each subsequent chemotherapy treatment.[34] These outcomes highlight the limited durability of current standard treatments beyond the first line and underscore the urgent need for more effective approaches, especially in HER2-low disease, where novel ADCs, such as T-DXd, has demonstrated promising efficacy.[18]

Currently, T-DXd is approved by the FDA for patients with unresectable or HER2-low (IHC 1+ or IHC 2+/ISH-negative) mBC who have received at least one prior chemotherapy in the metastatic setting or who have developed disease recurrence during or within six months of completing adjuvant chemotherapy.[37] In the DESTINY-Breast04 trial, the HER2-Low HR-positive group had a median PFS of 10.1 months with T-DXd and 5.4 months in the group receiving chemotherapy (hazard ratio, 0.51; $P < 0.001$).[18] This highlights the drug's potential to delay disease progression significantly, leading the NCCN guidelines to recommend T-DXd as a preferred second-line option for patients with HER2-low, HR-positive disease.[33]

T-DXd has demonstrated a manageable and tolerable safety profile across the DESTINY clinical program, with the most common AEs being low-grade hematologic and gastrointestinal AEs. However, it is associated with a risk of developing drug-induced interstitial lung disease/pneumonitis, which can be fatal. Regular monitoring for this serious side effect, diagnosis, and management are essential, along with carefully following specific guidelines for holding, discontinuing, and managing the drug.[38]

Taken together, these findings highlight the evolving landscape of mBC management and emphasize the critical role of precise tumor characterization in guiding therapeutic decisions. Accurate characterization of HER2-low disease has become critically important for identifying patients who may benefit from emerging HER2-targeted therapies such as T-DXd. In our cohort, although standardized scoring classified 66.4% of HER2-negative patients as HER2-low, only 51.6% were explicitly documented as HER2-low in routine pathology reports, and nearly 20% lacked any HER2 IHC-level documentation. These findings highlight a significant gap in pathology practice that could hinder timely patient access to emerging HER2-low–targeted treatments. Establishing standardized HER2 IHC assessment and reporting approaches across the GCC region is therefore essential to ensure that eligible patients are accurately identified and can access effective therapies, such as ADCs.

Strengths and limitations

Our study is among the largest multicenter, real-world studies in the GCC region, with a large sample size and data retrieved from ten sites across four countries. This enhances the generalizability of findings and their relevance to routine clinical practice and outcomes in the region. Although the study was retrospective, cases lacking clear HER2 IHC/ISH scoring in the original pathology reports were required to have archived tissue available for centralized HER2 re-evaluation, ensuring consistent classification according to current HER2-low definitions. However, this real-world study has limitations that should be acknowledged. The retrospective nature of the study precludes the establishment of causal relationships. In addition, our study didn't evaluate survival endpoints beyond the rwPFS, such as the OS.

Conclusion

This real-world, multicenter, retrospective observational study reveals the clinicopathological features of the HER2-low subtype of advanced and/or metastatic breast cancer and its significant prevalence in the GCC region. Our findings showed that despite the available lines of therapy, whether single agents or combinations, disease relapse continued to be a significant challenge. The median rwPFS for the first- and second-line therapies emphasizes the ongoing need for more effective treatment options to achieve better outcomes. This sheds light on the limitations of the traditional binary classification of BC patients into only two groups: HER2-positive and HER2-negative. With the development of new ADCs, such as T-DXd, the importance of detecting low levels of HER2 expression in routine clinical practice is increasing, ensuring that this patient subgroup has access to this targeted therapy and does not miss out on effective management.

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Conflict of interest

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