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ANATOMICAL PATHOLOGY

HER2-low breast cancer and response to neoadjuvant chemotherapy: a population-based cohort study

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Summary

About half of breast cancers (BC) without amplification of the human epidermal growth factor receptor 2 (HER2) have a low HER2 protein expression level (HER2-low). The clinical impact of HER2-low and the response to neoadjuvant chemotherapy (NAC) is unclear. This study aimed to assess the association between HER2-low BC and pathological response to NAC. Data from the Dutch Pathology Registry were collected for 11,988 BC patients treated with NAC between 2014 and 2022. HER2-low BC was defined as an immunohistochemical score of 1+ or 2+ and a negative molecular reflex test. We compared clinicopathological features of HER2-0 versus HER2-low BC and assessed the correlation between HER2 status and the pathological complete response (pCR) rate after NAC, including overall survival. Among hormone receptor (HR)-positive tumours, 67% (n=4,619) were HER2-low, compared to 47% (n=1,167) in the HR-negative group. Around 32% (n=207) of patients had a discordant HER2 status between the pre-NAC biopsy and the corresponding post-NAC resection, within which 87% (n=165) changed from HER2-0 to HER2-low or vice versa. The pCR rate was significantly lower in HER2-low BC compared to HER2-0 BC within the HR-positive group (4% versus 5%; p=0.022). However, the absolute difference was limited, so the clinical relevance is questionable. In HR-negative cases, the difference in pCR was not significant (32% versus 34%; p=0.266). No significant difference in overall survival was observed between HER2-low and HER2-0 tumours, regardless of hormone receptor status. The antibody-drug conjugate trastuzumab deruxtecan (T-DXd) has improved survival outcomes of patients with HER2-low metastatic BC. The finding that one-third of the patients in this study had a discordant HER2 status between the pre-NAC biopsy and the post-NAC resection specimen could impact clinical decision-making should T-DXd be used in early BC treatment.

Key words: HER2-low; breast cancer; antibody-drug conjugates; immunohistochemistry; neoadjuvant chemotherapy; pathological complete response.

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INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed cancer worldwide.[1] It is a heterogeneous disease that includes distinct biological entities with different oncogenic drivers and prognosis.[2,3] One surrogate molecular subtype of BC is characterised by overexpression [immunohistochemistry (IHC) score of 3+] or amplification of the human epidermal growth factor receptor 2 (HER2), which comprises approximately 15% of BC cases.[3,4] This subtype has been treated successfully for over two decades with anti-HER2 monoclonal antibodies.[5–7] However, these drugs have not been effective against tumours that have low expression levels of HER2 (HER2-low).[8] Currently, HER2-low tumours are defined as those with an IHC score of 1+ or 2+ with a negative molecular reflex test such as an *in situ* hybridisation result.[9] The HER2-low group corresponds to approximately half of HER2 non-amplified cases.[2]

The treatment landscape and the corresponding interest in levels of HER2 expression has changed in recent years with the introduction of a new group of drugs called antibody-drug conjugates.[10] The most promising clinical effect so far has been reported with trastuzumab-deruxtecan (T-DXd).[9,11,12] This compound consists of a humanised anti-HER2 monoclonal antibody linked to a membrane-permeable topoisomerase I inhibitor payload with short systemic half-life through a tetra-based cleavable linker.[13] In 2020, T-DXd was approved by the US Food and Drug Administration for use in pretreated BC patients with HER2 amplification.[10] In the recent DESTINY-Breast04 and DAISY clinical trials, T-DXd also showed antitumour activity against HER2-low tumours.[9,14] This drug can target tumour cells that express low levels of HER2 due to its unique topoisomerase payload, which causes a potent bystander killing effect. This demonstrated a prolonged progression-free survival and overall survival of patients with HER2-low tumours in comparison to standard chemotherapy.[9] Recently, T-DXd was conditionally authorised by the European Medicines Agency as the first HER2-directed therapy for patients with HER2-low metastatic BC.[9,15,16]

Considering the potential benefits of T-DXd in patients with HER2-low metastatic BC, the next step would be to explore its use in the early disease stage, including in the

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neoadjuvant setting. With current neoadjuvant chemotherapy (NAC) regimens, a high proportion of patients do not achieve a pathological complete response (pCR).[17] This has been associated with poorer survival in patients with luminal B and triple-negative BC (TNBC).[17–21] Since HER2-low BC constitutes a substantial proportion of BC cases, novel targeted neoadjuvant treatment options could have an impact on the pCR rate in HER2-low cases.

Only a few studies have investigated the association between HER2-low expression and response to NAC. In a pooled retrospective study from four clinical trials (n=2,310 patients treated with NAC), the pCR rate was significantly lower in HER2-low tumours compared to HER2-0 tumours in the general cohort and also in the hormone receptor (HR)-positive subgroup, but not in the TNBC group.[22] A retrospective single centre study (n=1,111 patients) reported similar results.[23] Recently, a very large retrospective study (n=1,136,016 patients from the US National Cancer Database) reported that pCR rates were significantly lower in HER2-low tumours, in both HR-positive and HR-negative patients.[24] In contrast, a smaller retrospective cohort (n=855 patients) did not report an association between HER2-low BC and pCR rate.[25]

In the current study, we compared the clinicopathological characteristics of HER2-low BC with HER2-0 cases and studied the association with pathological treatment response and overall survival, using real-world data from a large Dutch nationwide cohort.

METHODS

Data acquisition

We collected data from all patients with primary invasive BC who had received NAC with a post-NAC resection specimen reported via synoptic reporting in the Dutch Pathology Registry (PALGA) between 1 January 2014 and 30 September 2022.[26] The initiation date was selected based on the inclusion of NAC data in the PALGA protocol module from that year. This nationwide synoptic reporting module includes parameters within categorical variables instead of using free-text fields, which facilitates large-scale data analyses. We also included data from the pre-NAC needle biopsy by extending our search to a period of nine months before surgery.

Patient and tumour characteristics

We included all male and female patients over 18 years old who received NAC for invasive BC. Exclusion criteria involved patients who had received other types of neoadjuvant treatment (e.g., only hormone therapy) before the surgical procedure.

Several clinical characteristics were collected, including sex, age at diagnosis (date of core needle biopsy) and type of surgery (breast conserving surgery versus mastectomy). Histopathological features from the core needle biopsies included histological subtype (according to the World Health Organization),[27] histological grade according to Bloom and Richardson (including the number of mitoses),[28] oestrogen receptor (ER), progesterone receptor (PR) and HER2 status, and angioinvasion. ER and PR status was defined as positive if 10% or more of the cancer cells showed nuclear ER or PR staining, independent of intensity, according to the Dutch Guideline for Breast Cancer Treatment.[29] HER2 status was scored according to international guidelines,[30,31] although different local protocols were used regarding the type of reflex testing. In the synoptic reporting module, pathologists routinely report the HER2 IHC results (0, 1+, 2+ and 3+) and the type and result of the reflex test. For a subset of patients, the level of Ki-67 expression was also reported.[32] Data from the post-NAC resection specimens covered the treatment response and, if available, the post-NAC ER, PR and HER2 status.[33] A pCR was defined as no residual tumour in the breast nor the lymph nodes, according to international consensus.[33] Overall survival was defined as the time between the needle biopsy diagnosis and death from any cause.

Statistical analysis

Fig. 1 presents an overview of the numbers of cases included for analysis. Reclassification of tumours was performed according to HR status and HER2 status, establishing the surrogate molecular subtype. The groups were divided

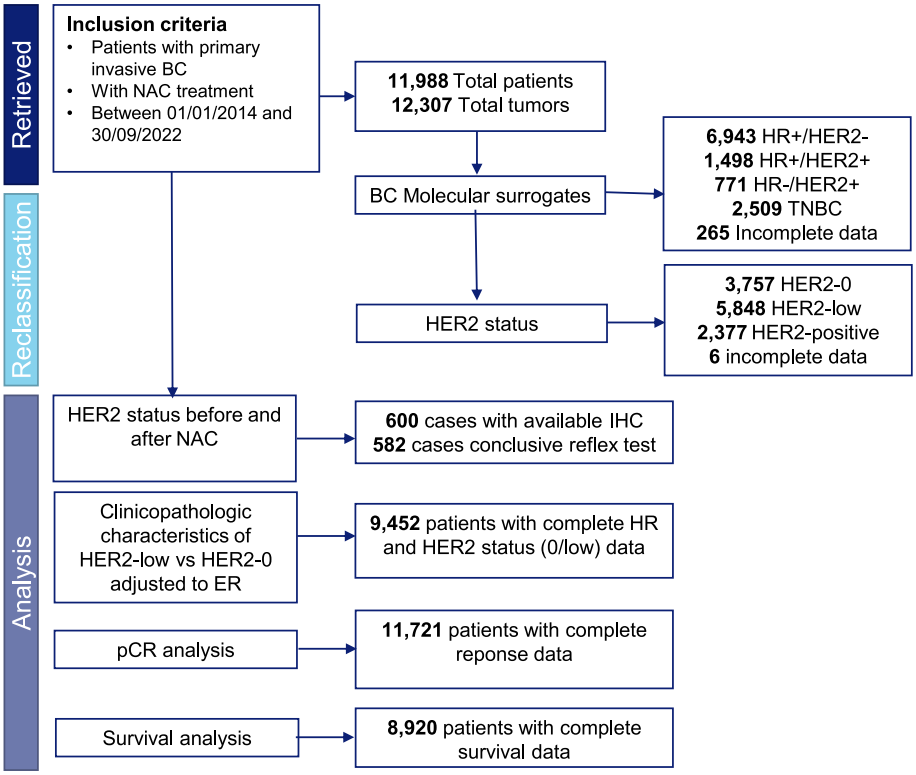

Fig. 1 Flow diagram of inclusion criteria for the subanalysis. BC, breast cancer; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; NAC, neoadjuvant chemotherapy; pCR, pathological complete response; TNBC, triple-negative breast cancer.

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as: (1) HR-positive (ER- and/or PR-positive)/HER2-negative; (2) HR-positive/HER2-positive; (3) HR-negative/HER2-positive; and (4) HR-negative/HER2-negative (TNBC). Additionally, we reclassified tumours with HER2 status as HER2-0 (HER2 IHC 0), HER2-low (IHC 1+ or 2+ with negative reflex test) and HER2-positive (IHC 2+ with positive reflex test or IHC 3+).

Relative and absolute frequencies of demographic and clinicopathological variables were calculated. The Kolmogorov–Smirnov test was used to calculate normality. Mean and standard deviation was calculated for normally distributed continuous variables, and median and interquartile range (IQR) (25th and 75th percentiles) was calculated for non-normally distributed variables. To estimate the difference in categorical and continuous variables between HER2-0 and HER2-low BC, adjusted to HR-positive and HR-negative, the Chi square test and Mann–Whitney test were applied. Sankey diagrams were used to depict the differences in HER2 IHC score and HER2 status (0, low, positive) from the core biopsy before NAC and the post-NAC resection specimen. Univariate and multivariate logistic regression models were used to assess associations between pCR and clinicopathological features (age, histology subtype, grade, number of mitoses, angioinvasion, HR and HER2 status). These variables were extracted from the pre-NAC core biopsy. We reported odds ratio and confidence intervals. Survival curves were generated through the Kaplan–Meier method. A two-sided log-rank test was employed to assess the differences in outcomes among groups. Patients who were alive were censored at the time of the most recent update of the database, which was 30 September 2022.

Tests were considered statistically significant when p values (two-tailed) were <0.05. The statistical analysis was performed in SPSS (IBM Corp, USA).

RESULTS

General patient and tumour characteristics

We retrieved data for 11,988 patients diagnosed with invasive BC between January 2014 and September 2022, which corresponded to 12,307 tumours. Most patients were women (99.7%). The median age at diagnosis was 57 years (IQR 49–66). Around 39% of patients underwent a mastectomy and 61% underwent a lumpectomy. In total, 96% (n=11,767) of the tumours had a known ER status based on the biopsy, from which 71% (n=8,386) were ER-positive and 29% (n=3,381) were ER-negative. Furthermore, 11,982 cases had a known HER2 status based on the biopsy: 31% (n=3,757) of the tumours were IHC 0, 33% (n=3,988) were IHC 1+, 19% (n=2,260) were IHC 2+ and 16% (n=1,977) were IHC 3+. After reclassification of the HER2 score using the result from the molecular reflex test, 31% (n=3,757) of the tumours were HER2-0, 49% (n=5,848) were HER2-low and 20% (n=2,377) were HER2-positive. Additionally, we classified the cases in surrogate molecular subtypes: 59% (n=6,945) were HR-positive/HER2-negative, 13% (n=1,498) were HR-positive/HER2-positive, 7% (n=771) were HR-negative/HER2-positive and 21% (n=2,509) were TNBC.

HER2 status before and after NAC

Of the 11,988 patients, only 5% (n=600) had complete ER and HER2 IHC data in both the pre-NAC core biopsy and the post-NAC resection specimen. Fig. 2A presents the comparison of HER2 IHC scores between the biopsy and the corresponding resection specimen after receiving NAC. In general, 56% (n=338) of the patients conserved their original IHC score in the resected specimen, while 44% (n=262) had a different score. Among the discordant scores, the majority (53%; n=138) shifted from IHC 0 in the biopsy to 1+ in the resection specimen (n=53), or vice versa (n=85). Only 5%

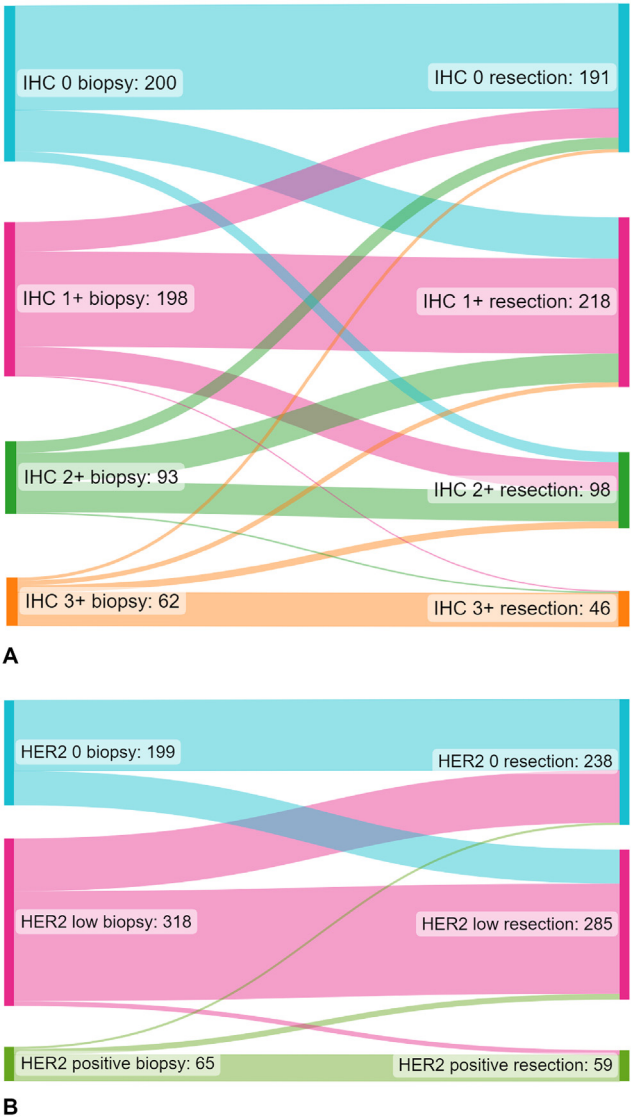

Fig. 2 Comparison of (A) human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) score (0, 1+, 2+, 3+) and (B) HER2 status (0, low, positive) in pre-neoadjuvant chemotherapy (NAC) core biopsy and the corresponding post-NAC resection specimen.

(n=13) of cases changed from IHC 0 in the biopsy to 2+ in the resection specimen. Additionally, 14% (n=37) of cases shifted from IHC 1+ in the biopsy to 2+ in the resection and 0.4% (n=1) changed from 1+ to 3+. Similarly, from the tumours that had a IHC score of 2+ in the biopsy, 6% (n=15) changed to IHC 0, 14% (n=37) to 1+ and 1% (n=2) to 3+. Finally, 7% (n=19) of the cases changed from IHC 3+ in the biopsy to IHC 0 (n=4), 1+ (n=6) or 2+ (n=9) in the resection.

Fig. 2B presents the differences in HER2 scores when reclassified as HER2-0, low and positive. From the 600 patients, we discarded 18 patients with IHC 2+ who had an inconclusive reflex test result. Of the 582 analysed cases, 68% (n=393) conserved the same HER2 category. From the cases that changed, 87% (n=165) changed from HER2-0 to HER2-low (n=65) or vice versa (n=100). Moreover, 8% (n=15) changed from HER2-positive to HER2-0 or HER2-low, and 5% (n=9) changed from HER2-0 or HER2-low to HER2-positive.

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Clinicopathological characteristics according to HER2 status

Table 1 lists the clinicopathological characteristics according to HER2 status (HER2-0, HER2-low, HER2-positive). In brief, HER2-low tumours were associated with older patients ($p<0.001$), lower histological grade ($p<0.001$), lower Ki-67 expression ($p<0.001$) and higher ER and PR expression ($p<0.001$) compared to HER2-0 and HER2-positive tumours.

Clinicopathological characteristics of HER2-low versus HER2-0 adjusted to ER

Based on the core biopsy, 9,452 patients had complete data regarding HR and HER2 status (0 or low). In total, 73% (n=6,943) of the patients were HR-postive, from which 33% (n=2,324) were HER2-0 and 67% (n=4,619) were HER2-low. In contrast, 27% (n=2,509) of the patients were HR-negative, from which 53% (n=1,342) were HER2-0 and 47% (n=1,167) were HER2-low.

In the HR-positive group, demographic characteristics such as age and type of surgery performed showed no significant differences between HER2-0 and HER2-low cases (Table 1). Regarding tumour characteristics, HER2-low tumours were more often classified as no special type (NST) with a lower proportion of lobular carcinomas ($p<0.001$). HER2-low tumours had a lower Ki-67 index ($p=0.037$) and had a slightly higher ER expression level ($p<0.001$) compared to HER2-0 cases. However, the absolute differences were limited.

On the other hand, within the HR-negative group, patients with HER2-low tumours were more often older than 50

Table 1 Clinicopathological characteristics (n, %) of human epidermal growth factor receptor 2 (HER2)-low and HER2-0 breast cancer according to hormone receptor (HR) status from core biopsy samples

Clinical and tumour characteristics	HR-positive (n=6,943)			HR-negative (n=2,509)		
	HER2-0 (n=2,324)	HER2-low (n=4,619)	p value univariate	HER2-0 (n=1,342)	HER2-low (n=1,167)	p value univariate
Age at diagnosis			0.523			**0.007**
<50 years	595 (25.6)	1150 (24.9)		457 (34.1)	339 (29)	
≥50 years	1729 (74.4)	3469 (75.1)		885 (65.9)	828 (71)	
Missing	0	0		0	0	
Type of surgery			0.555			0.894
Mastectomy	955 (41.1)	1864 (40.4)		483 (36)	423 (36.2)	
Lumpectomy	1369 (58.9)	2755 (59.6)		859 (64)	744 (63.8)	
Missing	0	0		0	0	
Histological type			**<0.001**			**<0.001**
NST	1250 (76.4)	2778 (82.7)		600 (91)	548 (93)	
Lobular	382 (23.3)	574 (17.1)		13 (2)	25 (4.2)	
Other	5 (0.3)	9 (0.3)		46 (7)	16 (2.7)	
Missing	687	1258		683	578	
Grade of invasive component			0.095			0.363
I	345 (23.8)	813 (26.8)		14 (2.5)	9 (1.8)	
II	888 (61.2)	1785 (58.8)		163 (29.6)	162 (33.3)	
III	219 (15.1)	437 (14.4)		374 (67.9)	316 (64.9)	
Missing	872	1584		791	680	
Angioinvasion			0.067			0.717
Yes	248 (14.6)	585 (16.9)		141 (18.3)	128 (19.2)	
Uncertain	64 (3.8)	147 (4.2)		18 (2.3)	12 (1.8)	
No	1385 (81.6)	2729 (78.9)		612 (79.4)	525 (78.9)	
Missing	627	3461		571	665	
Mitoses			0.663			0.606
Median (IQR)	3 (1–7)	3 (1–6)		14 (5–27)	14 (5–4)	
Missing	1241	2252		1015	872	
Ki-67			**0.037**			**0.009**
Median (IQR)	2 (1–5)	7 (5–15)		50 (27–71)	14 (5–60)	
Missing	2029	4481		1296	1146	
ER percentage			**<0.001**			**0.039**
Median (IQR)	100 (90–100)	100 (95–100)		0	0	
Missing	0	0		330[a]	224[a]	
ER expression levels			**<0.001**			n/d
0–9	32 (1.4)	19 (0.4)		1,002 (100)	943 (100)	
≥10–49	81 (3.5)	107 (2.3)		0	0	
≥50–100	2208 (96.5)	4492 (97.7)		0	0	
Missing	35	20		340[a]	224[a]	
PR percentage			0.686			**0.043**
Median (IQR)	80 (20–100)	80 (20–100)		0	0	
Missing	89	152		340[a]	226[a]	
PR expression levels			0.127			n/d
0–9	417 (18.7)	790 (17.7)		1002 (100)	941 (100)	
≥10–49	285 (12.8)	647 (14.5)		0	0	
≥50–100	1533 (68.6)	3030 (67.8)		0	0	
Missing	89	152		340[a]	226[a]	

ER, oestrogen receptor; IQR, interquartile range; n/d, not done; NST, no special type; PR, progesterone receptor.
Bold p values <0.05.
[a] Within the HR-negative group, some cases (ER=554, PR=566, both ER and PR=542) had a negative status described in the original pathology report but the specific percentage of ER and/or PR expression was missing.

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(p=0.007) compared to patients with HER2-0 tumours. HER2-low tumours were more often subtyped as NST (p<0.001) while in HER2-0 cases the proportion of other subtypes was higher. The majority (85%) of these special BC subtypes were classified as metaplastic carcinomas. In addition, HER2-low tumours had a lower Ki-67 percentage (p=0.009). According to the Mann–Whitney test, HER2-low tumours had slightly higher ER and PR expression compared to HER2-0 tumours (p=0.039 and p=0.043, respectively), although the median and IQR did not reflect this. In the HER2-low group, 81% (n=762) had an ER expression of 0% and 19% (n=181) had an ER expression of 1–9%. In HER2-0 BC, 84% (n=855) had an ER expression of 0% and 16% (n=157) had an expression of 1–9%. Likewise, in the HER2-low group, 86% (n=805) had a PR expression of 0%, and 14% (n=136) had an expression of 1–9%. In HER2-0 cases, 89% (n=891) had a PR expression of 0% and 11% (n=111) had an expression of 1–9%.

pCR in HER2-low versus HER2-0 BC, adjusted for HR status

pCR rates were obtained from 11,721 patients and then categorised according to their biopsy-based BC subtypes. The pCR rate was 4% (n=309/6,943) in HR-positive/HER2-negative patients, 31% (n=463/1,498) in HR-positive/HER2-positive cases, 60% (n=463/771) in HR-negative/HER2-positive cases and 33% (n=827/2,509) in TNBC patients.

In the general cohort, limited to non-amplified HER2 cases (n=9,452 patients), the pCR rate was significantly lower in HER2-low cases (9.5%, n=558) compared to HER2-0 cases (15.9%, n=599, p<0.001). Within the HR-positive group, this difference was also significant, with 3.9% (n=179) of HER2-low cases achieving a pCR versus 5.5% (n=128) of the HER2-0 cases (p=0.002). In the HR-negative group, the pCR rate was also lower in HER2-low cases (32%, n=374) compared to HER2-0 cases (33.8%, n=453), but this difference was not statistically significant (p=0.364) (Fig. 3).

As presented in Table 2, we further analysed the impact of clinicopathological characteristics on the pCR rate. In univariable logistic regression analysis, we found a significantly lower pCR rate in patients older than 50 compared to patients younger than 50. In addition, patients with angioinvasion had a lower pCR rate. A negative ER or PR status was associated with a higher pCR rate. HER2-low tumours had a lower pCR rate compared to HER2-0 tumours. After multivariable analysis, only age, angioinvasion, ER and PR status remained significantly associated with the chance of achieving a pCR.

Survival analysis in HER2-low versus HER2-0 BC, adjusted for HR status

From an initial cohort of 9,452 patients, we excluded 532 cases due to lack of complete follow up data. The final number of included patients for survival analysis was 6,671 patients within the HR-positive group and 2,306 within the HR-negative group. The overall median follow up was 34.5 months: 35.5 months in the HR-positive cohort and 31.5 months in the HR-negative cohort. In the overall survival analysis, Kaplan–Meier curves showed no significant differences between patients with HER2-0 and HER2-low BC, neither within the HR-positive cohort (HER2-0 73.8 versus HER2-low 75 months, p=0.476; Fig. 4A) nor in the HR-negative cohort (HER2-0 68 versus HER2-low 70.4 months, p=0.086; Fig. 4B).

We also assessed survival according to pCR status, stratified by HR status. Patients with a pCR had significantly better overall survival than patients without a pCR (p=0.025 for HR-positive cases and p<0.001 for HR-negative cases).

DISCUSSION

This study presents retrospective, non-centrally reviewed, real-world clinicopathological data and prognostic outcomes for patients with HER2-low BC treated with NAC. As reported in previous studies, the proportion of patients with HER2-low BC was higher in the HR-positive group compared to the HR-negative group (67% versus 47%).[23,25,34] Regarding the clinicopathological characteristics of HER2-low BC, we observed several statistically significant features

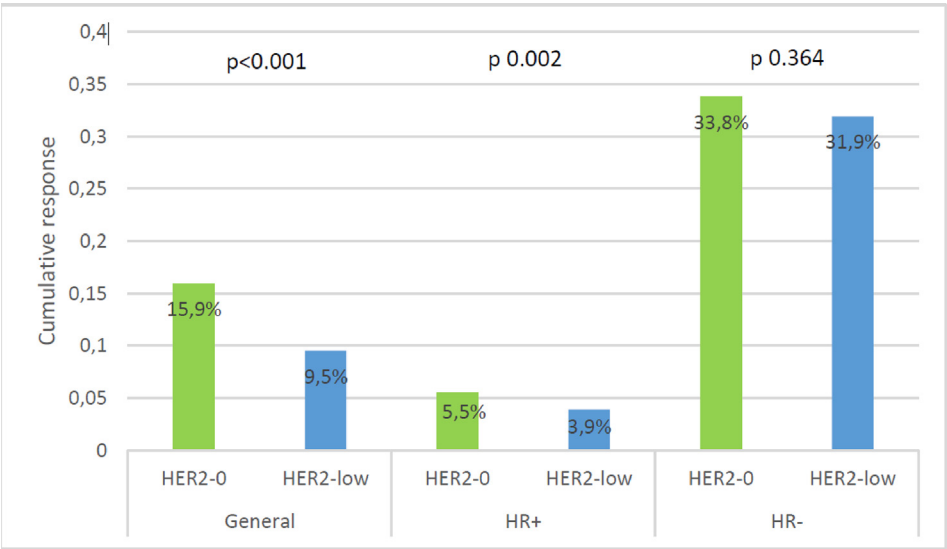

Fig. 3 Complete pathological response rates in human epidermal growth factor receptor 2-0 (HER2-0) versus HER2-low cases, adjusted for hormone receptor (HR) status.

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Table 2 Univariate and multivariate analysis of pathological features impacting the pathological complete response rate

Variable	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age						
<50 years	reference			reference		
≥50 years	0.51	0.45–0.58	**<0.001**	0.58	0.43–0.79	**<0.001**
Histology						
NST	reference	0.51–5.00	0.4			
Lobular and other	1.61					
Bloom Richardson grade						
G1	reference					
G2 and G3	2.99	0.38–23.18	0.29			
Mitoses						
<3	reference					
≥3	0.35	0.06–1.94	0.23			
Angioinvasion						
Not present	reference	0.42–0.92	**0.02**	reference	0.41–0.92	**0.018**
Present or uncertain	0.062			0.061		
ER status						
Positive	reference			reference		**<0.001**
Negative	11.13	9.64–12.84	**<0.001**	5.76	3.57–9.29	
PR status						
Positive	reference			reference		
Negative	8.23	7.08–9.77	**<0.001**	2.13	1.24–3.65	**0.006**
HER2 status						
HER2-0	reference			reference	0.57–1.01	0.067
HER2-low	0.55	0.49–0.63	**<0.001**	0.76		

CI, confidence interval; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; NST, no special type; OR, odds ratio, PR, progesterone receptor. Bold *p* values <0.05.

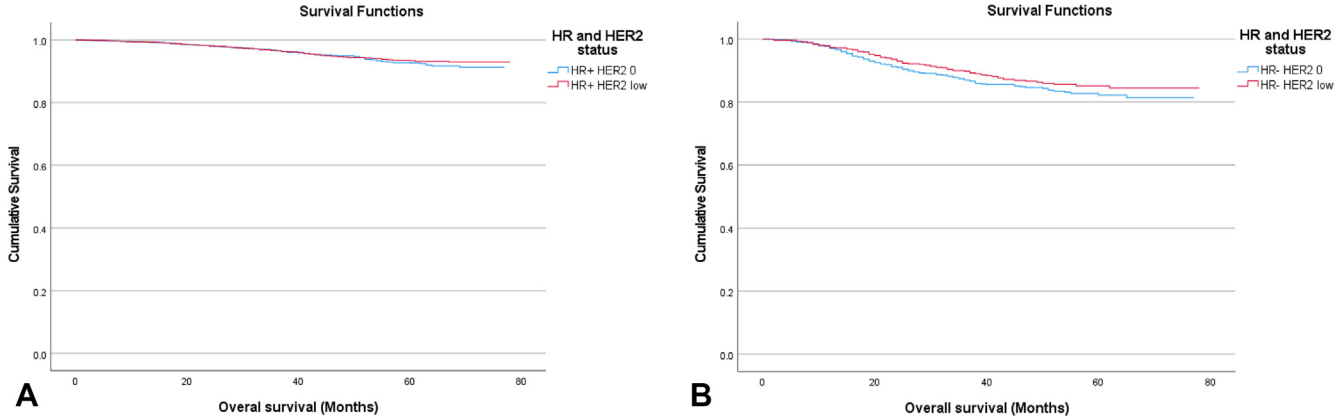

Fig. 4 Kaplan–Meier analysis of overall survival by human epidermal growth factor receptor 2 (HER2) status (0 vs low) in (A) hormone receptor (HR)-positive cases and (B) HR-negative cases.

within the HR-positive group, including a higher proportion of the NST subtype, a lower Ki-67 index and slightly higher ER expression compared to HER2-0 cases. These findings are in line with other reports and our previous study restricted to BC patients without pretreatment.[35–39] Within the HR-negative cohort, we found that HER2-low BC was associated with older age, NST histology, lower Ki-67 and a higher proportion of cases with an ER and PR expression of 1–9%, which is also consistent with our previous study and with other reports.[22,35,38,40,41] Notably, although statistical significance was achieved for several clinicopathological features within the HR-positive and HR-negative group, the absolute difference from many of these characteristics tends to be relatively small. Thus, their clinical relevance seems rather questionable, especially at the individual patient level.

HER2 IHC disagreement between the pre-NAC core biopsies and the corresponding post-NAC resection specimen was high. Approximately 44% of the cases exhibited a discordant IHC score between the biopsy and the resection, which decreased to 32% when the tumours were reclassified into HER2-0, low and positive categories. Among the cases with a discordant HER2 status, 8% (*n*=15) changed from HER2-amplified to HER2-non-amplified (either HER2-0 or HER2-low) and 5% (*n*=9) changed from non-amplified to amplified. This is consistent with other studies, reporting a change from HER2-amplified in the pre-NAC biopsy to

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HER2-non-amplified in the resection in up to 15% of patients.[42–45] The discordance rate (from HER2-amplified to HER2-non-amplified or vice versa) in our study may be attributed to patient selection bias, as HER2 is not routinely retested in the post-NAC resection specimen, in line with international guidelines.[31] However, since HER2 conversion could potentially impact post-NAC adjuvant treatment decisions, re-evaluation of HER2 on the post-NAC resection specimen should be considered, at least in those cases with poor treatment response.[46,47]

Discrepancies in HER2 status could also be explained by multiple other factors. A recent study by Kang *et al.* reported that ER-positive BC patients had a significantly higher probability of gaining HER2-low expression in the post-NAC resection specimen than ER-negative patients, which suggests that changes in the level of HER2 expression after anticancer treatment are related to HR positivity.[45] Furthermore, poor interobserver agreement of HER2 non-amplified cases has consistently been reported, even between specialist breast pathologists.[48–50] This is understandable because until very recently pathologists were mainly expected to discern between amplified and non-amplified cases.[51] The use of deep learning-based image analysis has shown high precision and reproducibility in several clinical trials.[52–54] However, limitations still exist, and no HER2 deep learning assay is yet available that has shown robustness if implemented in diverse hospital settings.[52–54]

Another explanation for HER2 discrepancy between pre-NAC and post-NAC is HER2 heterogeneity within the same tumour.[55–58] In a recent study by Yang *et al.* using next-generation sequencing, substantial genetic heterogeneity was found in HER2-low BC cases, mainly in the MAPK pathway. However, HER2-low BC showed few differences compared to HER2-0 BC in terms of gene or pathway changes.[58] Preanalytical factors such as delayed tumour fixation in the resection specimen could also play a role.[59,60]

The difference in HER2 expression between the pre-NAC needle biopsy and the post-NAC resection specimen could become clinically relevant should T-DXd be used in the treatment of early BC. Currently, the benefit of T-DXd has mainly been studied in HER2-low cases while data are limited in HER2-0 cases. Yet, the lower limit of clinically relevant HER2 expression remains unknown. The ongoing DESTINY-06 trial might provide some answers to that question.[61] The heterogeneity of HER2-low tumours and its impact on the response to T-DXd should be a matter of further research.

We evaluated the difference in pCR according to HR and HER2 status. Overall, HR-negative/HER2-positive patients, generally receiving NAC combined with neoadjuvant anti-HER2 therapy, had the highest cPR rate (60%). Within the HR-positive group, patients with HER2-low BC achieved a significantly lower pCR rate compared to HER2-0 cases. In the TNBC group, no statistical significance was seen. In the complementary logistic regression analysis, HER2-low status was associated with a lower pCR rate in univariate analysis, although in multivariate analysis the statistical significance was lost. Denkert *et al.* and de Nonneville *et al.* reported similar results, with HER2-low status having a negative impact in achieving a pCR in HR-positive tumours, which was not seen in TNBC.[22,23] However, a much larger retrospective American cohort reported a statistically lower pCR rate for HER2-low cases, in both HR-positive and ER-negative subgroups.[24] Some smaller cohorts have not found any association between HER2-low tumours and pCR in either group.[25,62,63]

These inconsistent results, mainly in TNBC cases, likely depend on sample size, wherein statistically significant results are only observed in extremely large cohorts. In these circumstances, the absolute differences between study subgroups are generally very subtle and their clinical relevance is therefore questionable. Another explanation for the current inconsistent results may be the intrinsic limitations of current diagnostic methods to discriminate between HER2-0 and HER2-low cases, as HER2 IHC is characterised by substantial interobserver variability.[48,49]

Regarding outcome, we found no statistical difference in overall survival between HER2-0 and HER2-low BC regardless of HR status, although HER2-low cases had a slightly better survival than HER2-0 cases in the HR-negative group. However, these results should be viewed with caution because of the short follow-up time. Previous studies have found conflicting results regarding survival. In two previous cohorts, patients with HER2-low BC had a significant longer overall survival than HER2-0 BC patients, but only within the HR-negative group.[22,24] In a French cohort, patients with HER2-low IHC 2+ BC had higher survival rates than patients with HER2 IHC 1+ BC, in both HR-positive and HR-negative groups.[63] Other studies did not find any difference in overall survival in either HR-positive or HR-negative cases.[23,34,38]

The reported survival difference in TNBC patients is in line with our finding of a lower Ki-67 index in HER2-low TNBC compared to HER2-0 TNBC. In our previous study, including BC patients without NAC, we also reported a significantly lower histological grade in HER2-low TNBC compared to HER2-0 TNBC,[38] but this difference in grade was not significant in the current study. The introduction of T-DXd in the NAC setting could possibly improve the survival of patients with HER2-low tumours. Future clinical trials should assess the potential benefits of the addition of T-DXd to neoadjuvant treatment regimens.

The findings of this study do not support the classification of HER2-low BC as a distinct biological entity. In particular, HER2-low tumours should not be regarded as a new surrogate molecular subtype. Certain favourable clinicopathological characteristics (including lower Ki-67 index and higher HR expression levels) were associated with HER2-low status, but the absolute differences were very small. Our results suggest that HER2-low status may be associated with a poorer response to NAC, which is consistent with previous reports.[22,24] However, the absolute differences in response between HER2-0 and HER2-low cases are limited, so the clinical relevance is uncertain. Besides, several confounding factors such as interobserver variation and preanalytical factors within a retrospective non-centrally reviewed cohort could have influenced our results.

The mechanism underlying the difference in treatment response may be related to the association between HER2-low and the level of ER expression.[62] As previously described by several authors, HER2-low tumours, particularly those within the HR-positive group, have a higher expression level of luminal-related genes. HER2-0 tumours, mostly within the TNBC group, tend to express more proliferation-related genes and tyrosine kinase receptor genes associated with the basal-like subtype.[50,64,65]

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The main strength of this study is that it is based on a large, nationwide cohort, which provides a real-world perspective of the clinical and prognostic factors of HER2-low BC treated with NAC. An important limitation of this study relates to its retrospective nature, including missing data and lack of central pathology revision, which limits the accurateness of the HER2-low category. Moreover, our study was based on a pathology registry, so clinical information including type of NAC (and type of anti-HER2 therapy in HER2-amplified cases), pre-NAC tumour diameter, nodal status and *BRCA* mutation status was missing. Another limitation is the short follow-up time, which weakens our outcome data.

In conclusion, around one-third of the BC patients in this study had a discordant HER2 status (0, low, positive) between the pre-NAC biopsy and the post-NAC resection specimen, which could impact clinical decision-making if T-DXd achieves a role in the treatment of early BC. In this retrospective, non-centrally reviewed dataset, HER2-low BC was associated with a lower pCR rate compared to HER2-0 cases in the HR-positive group, although the absolute difference was limited, and the clinical relevance is questionable. Treatment of HER2-low tumours with T-DXd in the NAC setting might change this, but the potential benefit of neoadjuvant treatment regimens with antibody-drug conjugates for patients with HER2-low BC remains to be elucidated in clinical trials.

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Ethics approval: According to the Code of Conduct of the Federation of Medical Sciences in the Netherlands, no informed consent or ethical approval was needed for this retrospective study. This study was performed in accordance with the Declaration of Helsinki. This study (MEC-2022-0677) was approved by the Medical Ethics Review Committee of Erasmus MC.

Data availability statement: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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