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Prevalence of HER2-low and IHC >0 to <1+ in breast cancer and its concordance between historical and rescored results: a multi-center, retrospective study in China

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Objective

- To evaluate the prevalence of different HER2 expression levels (especially HER2-low and HER2 IHC >0 to <1+population) in Chinese breast cancer patients.
  - ✓ To describe the histopathological and clinicopathological features across different HER2 expression levels.
- To characterize the concordance between historical and rescored results on HER2 expression levels.

Conclusions

- HER2-low prevalence in Chinese breast cancer patients was 54.5%, while 10.6% of patients were identified as HER2 IHC >0 to <1+, which is currently being investigated in a randomized controlled trial comparing T-DXd with SoC.
  - ✓ To our knowledge, this is the first study to report the prevalence of HER2-low and HER2 IHC >0 to <1+ in the Chinese breast cancer population based on rescored results.
  - ✓ Notably, the prevalence of HER2-low was numerically higher in the HR+ subgroup compared to the HR-subgroup (72.3% vs 54%).
- The concordance of HER2-low between the historical and rescored results was 91.7%, indicating historical results were relatively reliable for HER2-low population identification.

Plain language summary

Why did we perform this research?

Historically, HER2 status has been categorized as HER2-positive, defined as immunohistochemistry (IHC) 3+ or IHC 2+/in situ hybridization (ISH)+, and HER2-negative. However, approximately 60% of HER2-negative breast cancers have been identified as HER2-low, defined as IHC 2+/ISH- or IHC 1+. This subset of patients has emerged as a new targetable population, with trastuzumab deruxtecan showing improved treatment outcomes in this population. The lower threshold for HER2 expression that can benefit from HER2-directed antibody-drug conjugates (ADCs), such as HER2 IHC >0 to <1+, is still under investigation. Given the advancements in HER2-directed therapy, it is crucial to have accurate and consistent HER2 scoring to guide treatment decisions. Thus, the objective of this study was to determine the percentage of Chinese breast cancer patients who could be classified as HER2-low and have IHC >0 to <1+. Additionally, we analyzed the concordance between the rescored and historical results.

How did we perform this research?

Patients who were diagnosed with breast cancer and underwent surgery between July 2021 and July 2022 from 10 centers in China were included. Archived HER2 IHC slides from these patients were subjected to rescoring by a trained review committee, blinded to the historical scores. All slides were stained using Ventana 4B5 and scored following the ASCO/CAP 2018 guidelines, including the addition of the IHC >0<1+ as defined in the DESTINY-Breast 06 trial. The prevalence of the rescored HER2 status was calculated, and the concordance between the historical and rescored HER2 status was assessed using the Cohen's Kappa coefficient.

What were the findings of this research and what are the implications?

In this study, we found that 54.5% of patients had HER2-low breast cancer, and 10.6% had HER2 IHC >0<1+. Demographics, histopathological and clinicopathological information were consistent between HER2-low and HER2 IHC 0, with no notable discrepancies evident in any characteristic. When comparing the historical results with the rescores, we found a high concordance rate of 91.6% for HER2-low and 85.2% for HER2 IHC 0, indicating that historical HER2 results can be considered relatively reliable for the diagnosis of HER2-low.In conclusion, our study provides valuable insights into the prevalence of HER2-low and IHC >0<1+ in the Chinese breast cancer population. Additionally, it highlights the importance of recognizing the reliability of historical HER2 results for the diagnosis of HER2-low.

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Introduction

- The development of trastuzumab deruxtecan (HER2-directed antibody-drug conjugates [ADC], T-DXd) has changed the anti-HER2 treatment paradigm [1], with HER2-low (defined as IHC2+/ISH- or IHC1+) breast cancer providing a target for therapy.[2]
  - ✓ Limited data on HER2-low prevalence in the breast cancer patient population ranged from 42.8% to 59 %.[3,4]
  - ✓ Most studies on HER2-low prevalence were based on historical results.[3,4]
- The lower threshold for HER2 expression that can benefit from HER2-directed ADCs is still being investigated, such as HER2 IHC >0 to <1+ (defined as IHC 0 with incomplete and faint staining in ≤10% of tumor cells) in the DESTINY-Breast06 trial[5].
- Accurate determination of HER2 scores has become a critical topic in clinical discussions, given its clinical relevance to HER2-directed treatment strategies.
  - ✓ The historical scores were based largely on identifying HER2-positive (IHC3+ or IHC 2+/ISH+) populations, and it is unclear whether HER2-low expression could be accurately assessed.
  - ✓ In addition, inconsistent conclusions have been drawn regarding the concordance between historical HER2 expression interpretations and rescored results. [6,7]

Methods

Study Design:

- This multicenter, retrospective study (HER2-PATH, NCT05203458) included patients who were diagnosed with breast cancer and underwent surgery from 10 sites around China between July 2021 and July 2022. Patient samples were collected chronologically during the study duration.
- Archived HER2 IHC slides from these patients were subjected to rescoring by a review committee, blinded to the historical results.
  - ✓ All slides were stained using Ventana 4B5 and scored following the ASCO/CAP 2018 guidelines, including the addition of the HER2 IHC >0<1+ cut-off as defined in the DESTINY-Breast06 trial[5].
  - ✓ The review committee comprised of two readers and one adjudicator. The two readers independently evaluated each slide blinded to the historical scores. If their results matched, the recorded outcome was considered final. In cases of disagreement, the adjudicator made the final judgment.
  - ✓ Fluorescence in situ hybridization results were further collected for IHC 2+ cases.

Statistical Analysis:

- The prevalence of different HER2 expression levels were calculated.
- Overall agreement between historical and rescored results on HER2 expression levels was examined using the Cohen's Kappa coefficient.
  - ✓ Kappa equal or greater than 0.8 is often considered almost perfect agreement, Kappa between 0.8 and 0.6 is considered substantial agreement.[8]
- Demographics and histopathological /clinicopathological characteristics were summarized descriptively by different HER2 expression levels.

Results

- A total of 2869 patients were included in the analysis (Figure 1). The distribution of rescored HER2 IHC scores and expression levels is listed in Table 1.

Figure 1. Patient flow

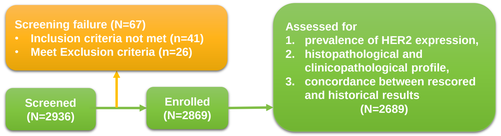

Table1. HER2 Expression levels based on the rescored results

Items	Total patients (N=2869)
HER2 IHC reassessed scores	
0	682 (23.8%)
IHC null	379 (13.2%)
IHC >0<1+	303 (10.6%)
1+	871 (30.4%)
2+	801 (27.9%)
3+	515 (18.0%)
Total	2869
FISH results for HER2 IHC reassessed scores with 2+	
FISH-	692 (86.6%)
FISH+	107 (13.4%)
Unavailable	2
Total	801
HER2 expression level based on the reassessed HER2 status	
HER2 IHC 0	682 (23.8%)
HER2-low	1563 (54.5%)
HER2-positive	622 (21.7%)
Unavailable	2
Total	2869

HER2-low is defined as IHC 1+ or IHC 2+/ISH-; HER2-positive is defined as IHC3+ or IHC 2+/ISH+.
HER2 IHC 0 comprises of IHC null and IHC >0<1+; IHC null, no discernible staining; HER2 IHC >0<1+ is defined as incomplete and faint staining in ≤10% of tumor cells.
The denominator of the percentage calculation is the total number of patients without missing data.

- Based on rescored HER2 status, the rates of HER2-positive, HER2-low, and HER2 IHC0 (including HER2 null and HER2 IHC >0 to <1+) were 21.7%, 54.5% and 23.8%, respectivel (Table 1).
  - ✓ Notably, the prevalence of HER2-low was numerically higher in the HR+ subgroup than HR− subgroup (72.3% vs 54%) (Table 2).

Table 2: Distribution of HER2 expression among different HR status

Items	HER2 IHC 0 (N=682)	HER2-low (N=1563)	HER2-positive (N=622)
ER status			
Positive	519 (76.1%)	1373 (87.9%)	352 (56.6%)
Negative	163 (23.9%)	189 (12.1%)	270 (43.4%)
Unavailable	0	1	0
Total	682	1563	622
PR status			
Positive	474 (69.5%)	1269 (81.2%)	274 (44.1%)
Negative	208 (30.5%)	294 (18.8%)	347 (55.9%)
Unavailable	0	0	1
Total	682	1563	622
HR status			
Positive	527 (77.3%)	1381 (88.4%)	367 (59.1%)
Negative	155 (22.7%)	182 (11.6%)	254 (40.9%)
Unavailable	0	0	1
Total	682	1563	622

- The prevalence of HER2 IHC >0 to <1+ was 10.6% among all patients and 42.0% among patients traditionally recognized as IHC 0, respectively.
  - ✓ Among the HR+ subgroup, the prevalence of HER2 IHC >0 to <1+ was 10.9%.
- Demographics, histopathological and clinicopathological information were consistent between HER2-low and HER2 IHC 0, with no notable discrepancies evident in any characteristic (Table 3).

Table 3. Patient histopathological and clinicopathological features across different HER2 expression levels in breast cancer

Items	HER2 IHC 0 (N=682)	HER2-low (N=1563)	HER2-positive (N=622)
Primary Tumor			
T0	1 (0.1%)	0 (0.0%)	0 (0.0%)
T1	301 (44.1%)	700 (44.8%)	228 (36.7%)
T2	271 (39.7%)	743 (47.5%)	334 (53.7%)
T3	16 (2.3%)	39 (2.5%)	18 (2.9%)
T4	0 (0.0%)	6 (0.4%)	2 (0.3%)
Tx	93 (13.6%)	72 (4.8%)	40 (6.4%)
Regional Lymph Nodes			
N0	412 (60.4%)	946 (60.5%)	383 (61.6%)
N1	134 (19.6%)	367(23.5%)	129 (20.7%)
N2	39 (5.7%)	118 (7.5%)	49 (7.9%)
N3	18 (2.6%)	69 (4.4%)	30 (4.8%)
NX	79 (11.6%)	63 (4.0%)	31 (5.0%)
Stage at initial diagnosis			
0	4 (2.4%)	2 (0.6%)	0 (0.0%)
I	53 (31.4%)	59 (16.8%)	25 (16.9%)
II	98 (58.0%)	247 (70.2%)	107 (72.3%)
III	13 (7.7%)	39 (11.1%)	16 (10.8%)
IV	1 (0.6%)	5 (1.4%)	0 (0.0%)
Unavailable	513	1211	474
Tumor size			
≤2 cm	362 (53.2%)	748 (48.2%)	242 (39.3%)
>2 cm	318 (46.8%)	804 (51.8%)	374 (60.7%)
Unavailable	2	11	6
Histologic types			
Invasive breast carcinoma of no special type	629 (92.2%)	1426 (91.2%)	583 (93.7%)
Other	53 (7.8%)	137 (8.8%)	39 (6.3%)
Histologic grade			
Well Differentiated (G1)	48 (7.0%)	153 (9.8%)	3 (0.5%)
Mod. Differentiated (G2)	379 (55.6%)	933 (59.7%)	223 (35.9%)
Poorly Differentiated (G3)	211 (30.9%)	407 (26.0%)	373 (60.0%)
Unassessable (GX)	44 (6.5%)	70 (4.5%)	23 (3.7%)

HER2-low is defined as IHC 1+ or IHC 2+/ISH-; HER2-positive is defined as IHC3+ or IHC 2+/ISH+.
HER2 IHC 0 comprises of IHC null and IHC >0<1+; IHC null, no discernible staining; HER2 IHC >0<1+ is defined as incomplete and faint staining in ≤10% of tumor cells.

- Overall, there was an 83.1% (Kappa, 0.77) concordance between the historical and rescored results for HER2 IHC scores (Table 4).
  - ✓ The concordance rate for IHC 1+ was numerically lower compared to other HER2 IHC scores. 12.1% of historically scored IHC 1+ patients were recategorized into IHC 2+, with limited impact on HER2-low diagnosis.

Table 4. Concordance between historical and rescored results on HER2 IHC scores

Items	HER2 IHC historical scores 0	1+	2+	3+	Total patients (N=2869)
HER2 IHC reassessed scores					
0	557(85.2%)	118 (13.5%)	7 (0.8%)	0 (0.0%)	682 (23.8%)
1+	96 (14.7%)	653 (74.5%)	121 (14.3%)	1 (0.2%)	871 (30.4%)
2+	1 (0.2%)	106 (12.1%)	688 (81.3%)	6 (1.2%)	801 (27.9%)
3+	0(0.0%)	0 (0.0%)	30 (3.5%)	485 (98.6%)	515 (18.0%)
Total	654	877	846	492	2869
Kappa coefficient(95% CI)	0.77 (0.75, 0.79)				

- For HER2 expression levels, the overall concordance rate between historical and rescored results was 91.7% (Kappa, 0.86; Table 5).
  - ✓ The concordance rate for HER2-low was 91.7%, suggesting discordant HER2 IHC scores had limited impact on HER2-low diagnosis.

Table 5. Concordance between historical and rescored results on HER2 expression

Items	HER2 IHC historical scores HER2 IHC 0	HER2-low	HER2-positive	Total patients (N=2869)
HER2 IHC reassessed scores				
HER2 IHC 0	557 (85.2%)	125 (7.8%)	0 (0.0%)	682 (23.8%)
HER2-low	97 (14.8%)	1461 (91.7%)	5 (0.8%)	1563 (54.5%)
HER2-positive	0 (0.0%)	8 (0.5%)	614 (99.2%)	622 (21.7%)
Unassessable	0	2	0	2
Total	654	1596	619	2869
Kappa coefficient (95% CI)	0.86 (0.85, 0.88)			

HER2-positive is defined as IHC3+ or IHC 2+/ISH+; HER2-low is defined as IHC 1+ or IHC 2+/ISH-.

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Disclosures

The authors have no competing financial interests to disclose that could have influenced the work reported in this poster.

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