PS4-08-01

Overall Survival and Breast-Cancer-Specific Survival in HER2-Low versus HER2-Zero Breast Cancer : A Single-Center Cohort Study

Min Jung Lee[1], Dong-Woo Choi[2], Heejung Chae[3,4], Jisun Kim[1], Jihyung Hong[3], Eun-Gyeong Lee[1], Jai Hong Han[1], Sung Hoon Sim[3], Seeyoun Lee[1], Keun Seok Lee[3], Han-Sung Kang[1], Hyun-Jin Kim[2], So-Youn Jung[1]

[1]Department of Surgery, Center for Breast Cancer, National Cancer Center, Goyang, Korea, [2]National Cancer Control Institute, National Cancer Center, Goyang, Korea

[3]Department of Internal Medicine, Center for Breast Cancer, National Cancer Center, Goyang, Korea, [4]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

Introduction

- Human epidermal growth factor receptor 2 (HER2)-low breast cancer (IHC 1+ or 2+ with ISH-negative) accounts for **40–50%** of all breast cancers.
- Therapeutic options for HER2-low disease are expanding; however, the **prognostic significance** of HER2-low compared to HER2-zero (IHC 0) remains **unclear and debated**.
- **The aim of this study is to** compare clinicopathologic characteristics and survival outcomes between **HER2-low** and **HER2-zero** breast cancers.

Methods and Materials

- Retrospective cohort study
- Inclusion criteria
  - Patients with pathologically confirmed breast cancer
  - National Cancer Center, Korea (2005-2023)
- Exclusion Criteria
  - No surgery
  - Metastasis
  - DCIS, clinical stage 0
  - Follow-up duration less than 1 year
  - Missing HER2 information or HER2-positive (IHC 3+)
- Endpoints
  - Overall Survival (OS)
  - Breast Cancer-Specific Mortality (BCSM)

Figure 1. Flow Chart

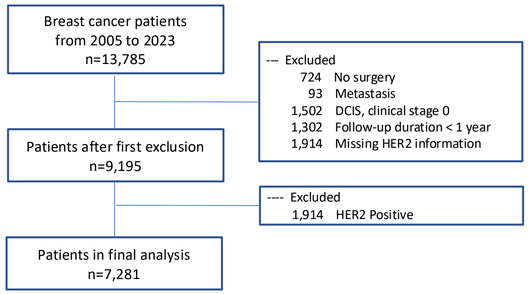


Table 1. Baseline characteristics by HER2 status and Hormone receptors

Variables	Overall				HR-Positive				HR-Negative			
	Total (7281)	HER-2		P-value	Total (6125)	HER-2		P-value	Total (1156)	HER-2		P-value
		Zero (2195, 30.1%)	Low (5086, 69.9%)			Zero (1626, 26.5%)	Low (4499, 73.5%)			Zero (569, 49.2%)	Low (587, 50.8%)	
Age at diagnosis, mean (SD), year	51.8 (±10.9)	51.7 (±11.2)	51.8 (±10.7)	0.590	51.6 (±10.7)	52.1 (11.3)	51.5 (±10.5)	0.240	52.4 (±11.7)	50.7 (±10.9)	54.0 (±12.2)	<0.001
BMI Mean (SD)												
<18	369 (5.1%)	120 (5.5%)	249 (4.9%)		300 (4.9%)	81 (5.0%)	219 (4.9%)		69 (6.0%)	39 (6.9%)	30 (5.1%)	
18-23	2,976 (40.9%)	888 (40.5%)	2,088 (41.1%)	0.560	2,502 (40.8%)	644 (39.6%)	1,858 (41.3%)	0.490	474 (41.0%)	244 (42.9%)	230 (39.2%)	0.130
>23	3,936 (54.1%)	1,187 (54.1%)	2,749 (54.1%)		3,323 (54.3%)	901 (55.4%)	2,422 (5.8%)		613 (53.0%)	286 (50.3%)	327 (55.7%)	
Histologic grade												
1-2	4,691 (64.4%)	1,238 (56.4%)	3,453 (67.9%)	<0.001	4,570 (74.6%)	1,191 (73.2%)	3,379 (75.1%)	0.300	121 (10.5%)	47 (8.3%)	74 (12.6%)	0.020
3	2,538 (34.9%)	936 (42.6%)	1,602 (31.5%)		1,516 (24.8%)	423 (26.0%)	1,093 (24.3%)		1,022 (88.4%)	513 (90.2%)	509 (886.7%)	
Unknown	52 (0.7%)	21 (1.0%)	31 (0.6%)		39 (0.6%)	12 (0.7%)	27 (0.6%)		13 (1.1%)	9 (1.6%)	4 (0.7%)	
T stage												
1	4,142 (56.9%)	1,241 (56.5%)	2,901 (57.0%)		3,610 (58.9%)	972 (59.8%)	2,638 (58.6%)		532 (46.0%)	269 (47.3%)	263 (44.8%)	
2	2,596 (35.7%)	824 (37.5%)	1,772 (34.8%)	0.004	2,086 (34.1%)	565 (34.7%)	1,521 (33.8%)	0.031	510 (44.1%)	259 (45.5%)	251 (42.8%)	0.021
3	376 (5.2%)	89 (4.1%)	287 (5.6%)		296 (4.8%)	58 (3.6%)	238 (5.3%)		80 (6.9%)	31 (5.4%)	49 (8.3%)	
Unknown	167 (2.3%)	41 (1.9%)	126 (2.5%)		133 (2.2%)	31 (1.9%)	102 (2.3%)		34 (2.9%)	10 (1.8%)	24 (4.1%)	
N stage												
0	4,525 (62.1%)	1,427 (65.0%)	3,098 (60.9%)		3,781 (61.7%)	1,025 (63.0%)	2,756 (61.3%)		744 (64.4%)	402 (70.7%)	342 (58.3%)	
1	1,831 (25.1%)	518 (23.6%)	1,313 (25.8%)	0.005	1,607 (26.2%)	414 (25.5%)	1,193 (26.5%)	0.270	224 (19.4%)	104 (18.3%)	120 (20.4%)	<0.001
2	634 (8.7%)	164 (7.5%)	470 (9.2%)		487 (8.0%)	115 (7.1%)	372 (8.3%)		147 (12.7%)	49 (8.6%)	98 (16.7%)	
Unknown	291 (4.0%)	86 (3.9%)	205 (4.0%)		250 (4.1%)	72 (4.4%)	178 (4.%)		41 (3.5%)	14 (2.5%)	27 (4.6%)	
Ki-67 (%)												
Mean (SD)	26.0 (±22.9)	31.1 (±26.3)	23.8 (±20.9)	<0.001	21.3 (±18.6)	22.9 (±20.9)	20.7 (±17.7)	0.160	51.1 (±26.8)	56.6 (±26.2)	47.7 (±27.0)	<0.001
Missing	371 (5.1%)	111 (5.1%)	260 (5.1%)		308 (5.0%)	80 (4.9%)	228 (5.1%)		63 (5.4%)	31 (5.4%)	32 (5.5%)	
Surgery												
BCS	6,590 (90.5%)	2,028 (92.4%)	4,562 (89.7%)	<0.001	5,541 (90.5%)	1,499 (92.2%)	4,042 (89.8%)	0.006	1,049 (90.7%)	529 (93.0%)	520 (88.6%)	0.011
Mastectomy	691 (9.5%)	167 (7.6%)	524 (10.3%)		584 (9.5%)	127 (7.8%)	457 (10.2%)		107 (9.3%)	40 (7.0%)	67 (11.4%)	
Chemotherapy												
No	2,839 (39.0%)	773 (35.2%)	2,006 (40.6%)	<0.001	2,688 (43.9%)	709 (43.6%)	1,979 (44.0%)	0.790	151 (13.1%)	64 (11.2%)	87 (14.8)	0.081
Yes	4,442 (61.0%)	1,422 (64.8%)	3,020 (59.4%)		3,437 (56.1%)	917 (56.4%)	2,520 (56.0%)		1,005 (86.9%)	505 (88.8%)	500 (85.2%)	
Adjuvant RT												
No	1,421 (19.5%)	428 (19.5%)	993 (19.5%)	1.000	1,228 (20.0%)	345 (21.2%)	883 (19.6%)	0.170	193 (16.7%)	83 (146.6%)	110 (18.7%)	0.069
Yes	5,860 (80.5%)	1,767 (80.5%)	4,093 (80.5%)		4,897 (80.0%)	1,281 (78.8%)	3,616 (80.4%)		963 (83.3%)	486 (85.4%)	477 (81.3%)	
Endocrine therapy												
No	1,392 (19.1%)	649 (29.6%)	743 (14.6%)	<0.001	236 (3.9%)	80 (4.9%)	156 (3.5%)	0.011	1,156 (100.0%)	569 (100.0%)	587 (100.0%)	-
Yes	5,889 (80.9%)	1,546 (70.4%)	4,343 (85.4%)		5,889 (96.1%)	1,546 (95.1%)	4,343 (96.5%)		0 (0.0%)	0 (0.0%)	0 (0.0%)	

Results

- HER2-low tumors demonstrated more favorable tumor biology than HER2-zero tumors, with higher rates of low histologic grade, low nuclear grade, and lower Ki-67 index (all p<0.001).
- Overall mortality was significantly lower in the HER2-low group (6.8% vs. 8.3%, p=0.031), although breast cancer-specific mortality was comparable (5.3% vs. 6.0%, p=0.091).
- Kaplan–Meier analysis showed no significant difference in OS between HER2 groups in the overall population (p=0.88).
- In HR-positive patients, HER2-low tumors retained favorable features and had lower all-cause (6.0% vs. 7.6%, p=0.034) and breast-cancer-specific mortality (4.2% vs. 4.8%, p=0.035), although OS was not significantly different (p=0.73).
- in HR-negative patients, HER2-low tumors showed no biologic advantage, higher (non-significant) mortality (13.1% vs. 10.4%, p=0.170), and significantly worse OS (p=0.02).
- Restricted cubic spline analysis showed rising mortality risk with increasing Ki-67 in the overall cohort. No interaction between HER2 status and Ki-67 was observed in the overall or HR-positive groups. In HR-negative patients, HER2-low tumors exhibited a U-shaped association with Ki-67, with elevated mortality at both low and high levels (p<0.01).

Figure 2. Kaplan–Meier and cumulative incidence curves for mortality according to HER2 status

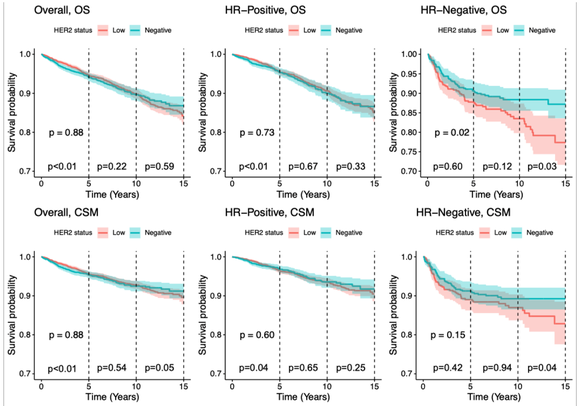


Figure 3. Association between Ki-67 levels and mortality using restricted cubic spline in Cox model

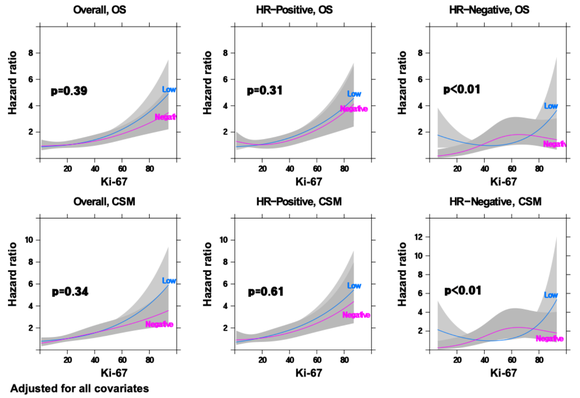


Table 2. Distribution of mortality by hormone receptors

Subgroup	HER2-Zero	HER2-Low	P-value
Overall			
All-cause death	182 / 2195 (8.3%)	348 / 5086 (6.8%)	0.031
BC-specific death	132 /2195 (6.0%)	253 / 5086 (5.0%)	0.091
HR-positive			
All-cause death	123 / 1626 (7.6%)	271 / 4499 (6.0%)	0.034
BC-specific death	78 / 1626 (4.8%)	191 / 4499 (4.2%)	0.035
HR-negative			
All-cause death	59 / 569 (10.4%)	77 / 587 (13.1%)	0.170
BC-specific death	54 / 569 (9.5%)	62 / 587 (10.6%)	0.070

Conclusion

- HER2-low status is not an independent prognostic factor in the overall or HR-positive breast cancer population but is associated with worse survival in HR-negative patients.
- Although Ki-67 is widely used to reflect tumor proliferation and prognosis, its predictive value may be limited in HR-negative, HER2-low tumors, suggesting the need for tailored prognostic strategies and potentially more aggressive treatment approaches in this challenging subgroup.
- Taken together, these findings underscore that the prognostic meaning of HER2-low is context dependent, and HR-negative HER2-low tumors likely represent a distinct biological entity requiring personalized risk stratification.
- Future research will need to incorporate multimodal biomarkers and novel composite risk models, and clinical trials may need to consider more aggressive or alternative therapeutic strategies specifically tailored to HR-negative HER2-low patients.

Funding

This study was supported by National Cancer Center, Korea (Grant No.: 2510432-1).

Contact

Min Jung Lee, MD
Center for Breast Cancer, National Cancer Center, Goyang, Korea
Email : jennmjlee@gmail.com

References

1. Hu, X., Yang, P., Chen, S. *et al.* Clinical and biological heterogeneities in triple-negative breast cancer reveals a non-negligible role of HER2-low. *Breast Cancer Res* **25**, 34 (2023).
2. Yang, M., Sun, J., Liu, L. *et al.* Clinicopathological characteristics of HER2-low breast cancer: a retrospective study. *Sci Rep* **13**, 12382 (2023).
3. Shaaban, A.M., Kaur, T.; Provenzano, E. HER2-Low Breast Cancer—Current Knowledge and Future Directions. *Medicina* **2021**, *57*, 644.
4. Yang, C., Zhang, X., Chen, Y. *et al.* Survival differences between HER2-0 and HER2-low-expressing breast cancer — a meta-analysis of early breast cancer patients. *Crit Rev Oncol Hematol* **185**, 103962 (2023).
5. de Moraes, F.C.A., de Castro Ribeiro, C.H.D., Peixoto, F.D.D.L. *et al.* Pathologic response rates in HER2-low versus HER2-zero early breast cancer patients receiving neoadjuvant therapy: a systematic review and meta-analysis. *Breast Cancer Res* **27**, 39 (2025).
6. Denkert, C., Seither, F., Schneeweiss, A. *et al.* Clinical and molecular characteristics of HER2-low-positive breast cancer: pooled analysis of individual patient data from four prospective neoadjuvant clinical trials. *Lancet Oncol* **22**, 1151–1161 (2021).
7. Tarantino, P., Gandini, S., Nicolò, E. *et al.* Evolution of low HER2 expression between early and advanced-stage breast cancer. *Eur J Cancer* **163**, 35–43 (2022).

This presentation is the intellectual property of the author/presenter. Contact them at jennmjlee@gmail.com for permission to reprint and/or distribute.

© Poster Template by Genigraphics® 1.800.790.4001 www.genigraphics.com