RESEARCH ARTICLE

Survival analysis in patients with invasive lobular cancer and invasive ductal cancer according to hormone receptor expression status in the Korean population

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Abstract

Background

We compared the clinicopathological characteristics and survival outcomes of invasive lobular carcinoma (ILC) cases with those of invasive ductal carcinoma (IDC) cases in various hormone receptor expression subgroups.

Methods

We compared clinicopathological characteristics, overall survival (OS), and breast cancer-specific survival (BCSS) between patients with IDC (n = 95,486) and ILC (n = 3,023). In addition, we analyzed the effects of different hormone receptor expression subgroups on survival.

Results

The ILC group had more instances of advanced stage and hormonal receptor positivity than did the IDC group (p < 0.001), but the IDC group had higher histological grade and nuclear grade, as well as higher frequency of human epidermal growth factor receptor 2 and Ki67 expression than did the ILC group (p < 0.001). The OS and BCSS were not significantly different between the IDC and ILC groups. The 5-year OS of the IDC group was 88.8%, while that of the ILC group was 90.6% (p = 0.113). The 5-year BCSS of the IDC group was 94.8%, while that of the ILC group was 95.0% (p = 0.552). When analyzing each hormone receptor expression subgroup, there were no significant differences in survival between the IDC and ILC groups. Moreover,
the hazard ratio of ILC in the ER negative/PR negative subgroup was 1.345 (95% confidence interval: 1.012–1.788; p = 0.041).

**Conclusions**

Hormone receptor expression should be considered when determining prognosis and treatment regimen for IDC and ILC. Researchers should further study the ER negative/PR negative population to identify treatment and prognostic models that will facilitate the development of individualized therapy for these patients, which is needed for good outcomes.

**Introduction**

In Korea, just as in western countries, the prevalence of breast cancer is increasing [1–4], and invasive breast cancer accounts for most cases [5]. Several studies comparing invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) have been conducted worldwide [6–10]; these have shown that ILC cases have similar or better survival outcomes compared to those of IDC cases, which account for most invasive breast cancer cases [8–12].

As individualized therapy has become important, studies on hormone receptor expression subtypes have been conducted, mainly in the West. According to the Surveillance, Epidemiology, and End Results (SEER) Program database, compared to IDC, ILC is associated with larger tumor size, older diagnosis age, advanced stage, lower histological grade, higher estrogen receptor (ER)/progesterone receptor (PR) expression, and lower human epidermal growth factor receptor 2 (HER-2) expression. Higher percentages of lymph node positivity and distant metastasis are also found in ILC cases than in IDC cases. In an analysis of hormone receptor expression status that excluded the ER negative/PR negative subgroup, the ER positive/PR positive subgroup showed the best survival, while the ER positive/PR negative subgroup had the worst outcomes [6].

As in the West, studies are being conducted in Asia, including Korea [13–15]. However, few have compared invasive breast cancer survival outcomes among different hormone receptor expression subgroups. Therefore, in the present work, we conducted a study on invasive breast cancer in Korea using data from the Korean Breast Cancer Registry (KBCR) to compare and analyze survival among various hormone receptor expression subgroups.

**Materials and methods**

**Ethical approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

**Patient selection**

In the KBCR database, we identified 98,509 patients with invasive breast cancer diagnosed between 2001 and 2013 who aged more than 18 years old. The KBCR database is a nationwide, Korean, multi-institutional online database. The Korean Breast Cancer Society (KBCS) prospectively keeps the information of patients diagnosed with breast cancer in 102 hospitals. The following information is included: patient identification number, age at operation, sex, tumor
stage based on the American Joint Committee on Cancer classification, pathophysiology, and type of surgery. Expression of ER and PR was considered positive if more than 10% of the tumor stained positive, HER-2 status was evaluated using HER-2 overexpression analysis with any grade over 2+ being considered positive. Fluorescence in situ hybridization was used when HER-2 status was graded as 2+, and considered positive if graded 3+ for its result. We excluded patients with metastatic breast cancer at the time of diagnosis, as well as those with carcinoma in situ or poorly evaluated axillary lymph nodes, and those without biological subtype information [S1 Table]. This study was approved by the Institutional Review Board of Asan Medical Center, Seoul, South Korea (20171341). Given that the study was based on retrospective clinical data, the need for informed consent was waived.

**Statistical analysis**

The clinicopathological features of invasive breast cancer cases were analyzed using a Pearson’s chi-square test. We used the Kaplan–Meier method and log-rank test to analyze and compare survival outcomes. Overall survival (OS) was defined as the time from the date of breast cancer diagnosis until the date of death (from any cause) or last follow-up. Breast cancer-specific survival (BCSS) was defined as the time from the date of breast cancer diagnosis until the date of breast cancer-related death or last follow-up. A Cox proportional hazard analysis was used to obtain hazard ratios (HRs) with 95% confidence intervals (CIs) in uni- and multivariable analyses. All p-values less than 0.05 were considered statistically significant. We used SPSS statistical software, version 26.0 (SPSS Inc., Chicago, USA) for all statistical analysis.

**Results**

**Clinicopathological characteristics of patients with invasive breast cancer**

In total, 98,509 patients diagnosed with invasive breast cancer between 2001 and 2013 were selected from the KBCR database, and their data were analyzed. Among them, 95,486 (96.9%) patients had IDC and 3,023 (3.1%) had ILC. The clinicopathological characteristics of the study population are summarized in Table 1. Patients with ILC were older at the time of surgery than those with IDC (≥41 years of age at operation: ILC group, 89.3% vs. IDC group, 81.5%; p < 0.001). Compared to the IDC group, the ILC group more frequently presented with advanced stage and positive ER and PR expression (p < 0.001). The IDC group had higher histological grade and nuclear grade as well as higher frequency of HER-2 and Ki67 expression than did the ILC group (p < 0.001).

In Table 2, we have compared the clinicopathological characteristics of the study population according to the hormonal receptor expression subgroups. The ER negative (−)/PR− group presented much higher histological grade and nuclear grade, as well as higher frequency of HER-2 and Ki67 expression than did other groups (p < 0.001). Regarding TNM stage, the ER positive (+)/PR+ subgroup was the least advanced, while the ER−/PR+ subgroup was the most advanced (p < 0.001). Patients in the ER−/PR+ were the oldest and showed the highest frequency of lymphovascular invasion (p < 0.001).

**Comparing survival outcomes of invasive breast cancer**

The median follow-up period of the study population was 76.9 months (range: 0.1–304 months). Fig 1 shows no significant differences in survival between the IDC and ILC groups. The 5-year OS of the IDC group was 88.8%, while that of the ILC group was 90.6% (p = 0.113). The 5-year BCSS of the IDC group was 94.8%, while that of the ILC group was 95.0% (p = 0.552).
Table 1. Clinicopathological characteristics of patients with invasive breast cancer.

| Characteristics       | Total (n = 98509) | IDC group (n = 95486) | ILC group (n = 3023) | p-value |
|-----------------------|------------------|-----------------------|----------------------|---------|
| **Age at operation**  |                  |                       |                      |         |
| ≤ 40                  | 17998 (18.3)     | 17674 (18.5)          | 324 (10.7)           | < 0.001 |
| ≥ 41                  | 80511 (81.7)     | 77812 (81.5)          | 2699 (89.3)          |         |
| **T stage**           |                  |                       |                      |         |
| 0                     | 115 (0.1)        | 112 (0.1)             | 3 (0.1)              | < 0.001 |
| 1                     | 55219 (56.1)     | 53756 (56.3)          | 1463 (48.4)          |         |
| 2                     | 38045 (38.6)     | 36786 (38.5)          | 1259 (41.6)          |         |
| 3                     | 4212 (4.3)       | 3933 (4.1)            | 277 (9.2)            |         |
| 4                     | 918 (0.9)        | 897 (0.9)             | 21 (0.7)             |         |
| **N stage**           |                  |                       |                      |         |
| 0                     | 63061 (64.0)     | 61099 (64.0)          | 1962 (64.9)          | 0.018   |
| 1                     | 25387 (25.8)     | 24664 (25.8)          | 723 (23.9)           |         |
| 2                     | 6824 (6.9)       | 6608 (6.9)            | 216 (7.1)            |         |
| 3                     | 3237 (3.3)       | 3115 (3.3)            | 122 (4.0)            |         |
| **TNM stage**         |                  |                       |                      |         |
| I                     | 42209 (42.9)     | 41032 (43.0)          | 1177 (38.9)          | < 0.001 |
| II                    | 44492 (45.2)     | 43090 (45.1)          | 1402 (46.4)          |         |
| III                   | 11786 (12.0)     | 11342 (11.9)          | 444 (14.7)           |         |
| Unknown               | 22               | 22                    | 0                    |         |
| **Histologic grade**  |                  |                       |                      |         |
| G1                    | 14880 (17.4)     | 14411 (17.3)          | 469 (24.7)           | < 0.001 |
| G2                    | 39257 (46.0)     | 38079 (45.7)          | 1178 (62.1)          |         |
| G3                    | 31163 (36.5)     | 30914 (37.1)          | 249 (13.1)           |         |
| Unknown               | 13209            | 12082                 | 1127                 |         |
| **Nuclear grade**     |                  |                       |                      |         |
| G1                    | 8675 (11.7)      | 8211 (11.3)           | 464 (24.4)           | < 0.001 |
| G2                    | 36776 (49.5)     | 35597 (49.1)          | 1179 (62.0)          |         |
| G3                    | 28909 (38.9)     | 28649 (39.5)          | 260 (13.7)           |         |
| Unknown               | 24149            | 23029                 | 1120                 |         |
| **LVI**               |                  |                       |                      |         |
| Negative              | 54057 (68.6)     | 51991 (68.1)          | 2066 (82.2)          | < 0.001 |
| Positive              | 24768 (31.4)     | 24321 (31.9)          | 447 (17.8)           |         |
| Unknown               | 19684            | 19174                 | 510                  |         |
| **Hormone expression**|                  |                       |                      |         |
| ER+/PR+               | 50367 (54.1)     | 48211 (53.4)          | 2156 (73.8)          | < 0.001 |
| ER+/PR−               | 11078 (11.9)     | 10660 (11.8)          | 418 (14.3)           |         |
| ER−/PR+               | 4372 (4.7)       | 4270 (4.7)            | 102 (3.5)            |         |
| ER−/PR−               | 27327 (29.3)     | 27082 (30.0)          | 245 (8.4)            |         |
| Unknown               | 5365             | 5263                  | 102                  |         |
| **HER2**              |                  |                       |                      |         |
| Negative              | 67276 (79.4)     | 64753 (78.9)          | 2523 (93.9)          | < 0.001 |
| Positive              | 17503 (20.6)     | 17338 (21.1)          | 165 (6.1)            |         |
| Unknown               | 13730            | 13395                 | 335                  |         |
| **Ki67**              |                  |                       |                      |         |
| < 20                  | 26933 (62.4)     | 25713 (61.6)          | 1220 (85.7)          | < 0.001 |
| > 20                  | 16247 (37.6)     | 16044 (38.4)          | 203 (14.3)           |         |
| Unknown               | 55329            | 53729                 | 1600                 |         |

(Continued)
In Fig 2, we analyzed the comparison of 5-year survival outcomes among hormone receptor expression subgroups in the total population. The ER+/PR+ subgroup showed the best 5-year survival (OS: 96.1%, BCSS: 98.5%) followed by the ER+/PR− subgroup (OS: 92.8%, BCSS: 96.7%), ER−/PR+ subgroup (OS: 90.5%, BCSS: 94.7%), and ER−/PR− subgroup (OS: 87.8%, BCSS: 91.7%; p < 0.001 for both OS and BCSS).

Similarly, as shown in Fig 3, the ER+/PR+ subgroup had the best survival, while the ER−/PR− subgroup had the worst in both the IDC and ILC groups (5-year OS in the IDC group: ER+/PR+, 88.9%; ER+/PR−, 83.0%; ER−/PR+, 83.4%; ER−/PR−, 81.9%; p < 0.001; 5-year BCSS of the IDC group: ER+/PR+, 96.1%; ER+/PR−, 93.2%; ER−/PR+, 91.8%; ER−/PR−, 92.0%; p < 0.001; 5-year OS of the ILC group: ER+/PR+, 88.0%; ER+/PR−, 80.3%; ER−/PR+, 82.2%; ER−/PR−, 74.4%; p < 0.001; 5-year BCSS of the ILC group: ER+/PR+, 95.6%; ER−/PR−, 90.1%; ER−/PR+, 88.8%; ER−/PR−, 87.1%; p < 0.001).

In the total population, ER−/PR− status conferred the highest risk on OS (HR: 1.620, 95% CI: 1.528–1.718; p < 0.001), followed by ER+/PR− status (HR: 1.419, 95% CI: 1.331–1.513; p < 0.001), ER−/PR+ status (HR: 1.344, 95% CI: 1.237–1.459; p < 0.001), and ER−/PR+ status (reference). Moreover, ER−/PR− status conferred the highest risk on BCSS among the total population (HR: 1.915, 95% CI: 1.747–2.098; p < 0.001), followed by ER−/PR+ status (HR: 1.625, 95% CI: 1.435–1.841; p < 0.001), ER+/PR+ status (HR: 1.516, 95% CI: 1.364–1.685; p < 0.001), and ER+/PR− status (reference). In the IDC group, the order of HR by hormone receptor expression was similar to that in the total population. In contrast, in the ILC group,
Table 2. Clinicopathological characteristics of hormonal expression subgroups in the total study population.

| Characteristics         | Total population |
|-------------------------|------------------|
|                         | ER+/PR+(n = 50367) | ER+/PR−(n = 11078) | ER−/PR+(n = 4372) | ER−/PR−(n = 27327) | p-value   |
| Age at operation        |                  |                  |                  |                  |           |
| ≤ 40                    | 8722 (17.3)      | 1565 (14.1)      | 979 (22.4)       | 5390 (19.7)       | < 0.001   |
| ≥ 41                    | 41645 (82.7)     | 9513 (85.9)      | 3393 (77.6)      | 21937 (80.2)      |           |
| T stage                 |                  |                  |                  |                  |           |
| 0                       | 27 (0.1)         | 21 (0.2)         | 2 (0.0)          | 59 (0.2)          | < 0.001   |
| 1                       | 31135 (61.8)     | 6323 (57.1)      | 1972 (45.1)      | 13326 (48.8)      |           |
| 2                       | 17223 (34.2)     | 4115 (37.1)      | 2063 (47.2)      | 12199 (44.6)      |           |
| 3                       | 1688 (3.4)       | 484 (4.4)        | 280 (6.4)        | 1398 (5.1)        |           |
| 4                       | 294 (0.6)        | 135 (1.2)        | 55 (1.3)         | 345 (1.3)         |           |
| N stage                 |                  |                  |                  |                  |           |
| 0                       | 32345 (64.2)     | 6877 (62.1)      | 2556 (58.5)      | 17858 (65.3)      | < 0.001   |
| 1                       | 13392 (26.6)     | 2979 (26.9)      | 1241 (28.4)      | 6347 (23.2)       |           |
| 2                       | 3168 (6.3)       | 862 (7.8)        | 399 (9.1)        | 1993 (7.3)        |           |
| 3                       | 1462 (2.9)       | 360 (3.2)        | 176 (4.0)        | 1129 (4.1)        |           |
| TNM stage               |                  |                  |                  |                  |           |
| I                       | 23693 (47.0)     | 4752 (42.9)      | 1457 (33.3)      | 10414 (38.1)      | < 0.001   |
| II                      | 21412 (42.5)     | 4859 (43.9)      | 2220 (50.8)      | 13230 (48.4)      |           |
| III                     | 5261 (10.4)      | 1463 (13.2)      | 694 (15.9)       | 3677 (13.5)       |           |
| Unknown                 | 5027             | 1192             | 763              | 3393              |           |
| Histologic grade        |                  |                  |                  |                  |           |
| G1                      | 11285 (24.9)     | 1652 (16.7)      | 444 (12.3)       | 971 (4.1)         | < 0.001   |
| G2                      | 24339 (53.7)     | 5140 (52.0)      | 1503 (41.6)      | 7006 (29.3)       |           |
| G3                      | 9716 (21.4)      | 3094 (31.3)      | 1662 (46.1)      | 15957 (66.7)      |           |
| Unknown                 | 5027             | 1192             | 763              | 3393              |           |
| Nuclear grade           |                  |                  |                  |                  |           |
| G1                      | 5846 (14.5)      | 1012 (11.8)      | 330 (11.5)       | 1180 (5.6)        | < 0.001   |
| G2                      | 24565 (61.1)     | 4591 (53.4)      | 1220 (42.5)      | 5493 (26.1)       |           |
| G3                      | 9768 (24.3)      | 2996 (34.8)      | 1323 (46.0)      | 14346 (68.3)      |           |
| Unknown                 | 10188            | 2479             | 1499             | 6308              |           |
| LVI                     |                  |                  |                  |                  |           |
| Negative                | 29567 (68.9)     | 6258 (68.9)      | 1898 (61.6)      | 15324 (69.6)      | < 0.001   |
| Positive                | 13344 (31.1)     | 2822 (31.1)      | 1182 (38.4)      | 6692 (30.4)       |           |
| Unknown                 | 7456             | 1998             | 1292             | 5311              |           |
| HER2                    |                  |                  |                  |                  |           |
| Negative                | 40713 (87.7)     | 7808 (78.0)      | 2674 (73.9)      | 15868 (64.9)      | < 0.001   |
| Positive                | 5712 (12.3)      | 2198 (22.0)      | 945 (26.1)       | 8589 (35.1)       |           |
| Unknown                 | 3942             | 1072             | 753              | 2870              |           |
| Ki67                    |                  |                  |                  |                  |           |
| ≤ 20                    | 18369 (74.2)     | 3158 (68.0)      | 694 (51.4)       | 4624 (37.6)       | < 0.001   |
| > 20                    | 6389 (25.8)      | 1485 (32.0)      | 656 (48.6)       | 7684 (62.4)       |           |
| Unknown                 | 25609            | 6435             | 3022             | 15019             |           |
| Chemothrapy             |                  |                  |                  |                  |           |
| No                      | 15274 (33.3)     | 2991 (30.3)      | 602 (15.6)       | 3109 (12.5)       | < 0.001   |
| Yes                     | 30561 (66.7)     | 6887 (69.7)      | 3261 (84.4)      | 21735 (87.5)      |           |
| Unknown                 | 4532             | 1200             | 509              | 2483              |           |

(Continued)
### Table 2. (Continued)

| Characteristics | Total population |
|-----------------|------------------|
| **Age at operation** | | |
| < 40 | 8494 (17.6) | 1542 (14.5) | 962 (22.5) | 5362 (19.8) | < 0.001 |
| ≥ 41 | 39717 (82.4) | 9118 (85.5) | 3308 (77.5) | 21720 (80.2) | |
| **T stage** | | | | | |
| 0 | 26 (0.1) | 21 (0.2) | 2 (< 0.1) | 59 (0.2) | < 0.001 |
| 1 | 30069 (62.4) | 6119 (57.4) | 1930 (45.2) | 13227 (48.8) | |
| 2 | 16330 (33.9) | 3957 (37.1) | 2012 (47.1) | 12084 (44.6) | |
| 3 | 1502 (3.1) | 436 (4.1) | 271 (6.3) | 1370 (5.1) | |
| 4 | 284 (0.6) | 127 (1.2) | 55 (1.3) | 342 (1.3) | |
| **N stage** | | | | | |
| 0 | 30927 (64.1) | 6596 (61.9) | 2501 (58.6) | 17712 (65.4) | < 0.001 |
| 1 | 12859 (26.7) | 2896 (27.2) | 1212 (28.4) | 6293 (23.2) | |
| 2 | 3039 (6.3) | 825 (7.7) | 387 (9.1) | 1964 (7.3) | |
| 3 | 1386 (2.9) | 343 (3.2) | 170 (4.0) | 1113 (4.1) | |
| **TNM stage** | | | | | |
| I | 22834 (47.4) | 4579 (43.0) | 1428 (33.5) | 10337 (38.2) | < 0.001 |
| II | 20390 (42.3) | 4688 (44.0) | 2167 (50.8) | 13119 (48.5) | |
| III | 4986 (10.3) | 1389 (13.0) | 674 (15.8) | 3620 (13.4) | |
| **Histologic grade** | | | | | |
| 1 | 1 | 4 | 1 | 6 | |

ALND, axillary lymph node dissection; BCS, breast conserving surgery; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LVI, lymphovascular invasion; PR, progesterone receptor; SNB, sentinel node biopsy; TM, total mastectomy.

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### Table 2–1. Clinicopathological characteristics of hormonal expression subgroups in the IDC group.

| Characteristics | IDC group |
|-----------------|-----------|
| **Age at operation** | | |
| < 40 | 8494 (17.6) | 1542 (14.5) | 962 (22.5) | 5362 (19.8) | < 0.001 |
| ≥ 41 | 39717 (82.4) | 9118 (85.5) | 3308 (77.5) | 21720 (80.2) | |
| **T stage** | | | | | |
| 0 | 26 (0.1) | 21 (0.2) | 2 (< 0.1) | 59 (0.2) | < 0.001 |
| 1 | 30069 (62.4) | 6119 (57.4) | 1930 (45.2) | 13227 (48.8) | |
| 2 | 16330 (33.9) | 3957 (37.1) | 2012 (47.1) | 12084 (44.6) | |
| 3 | 1502 (3.1) | 436 (4.1) | 271 (6.3) | 1370 (5.1) | |
| 4 | 284 (0.6) | 127 (1.2) | 55 (1.3) | 342 (1.3) | |
| **N stage** | | | | | |
| 0 | 30927 (64.1) | 6596 (61.9) | 2501 (58.6) | 17712 (65.4) | < 0.001 |
| 1 | 12859 (26.7) | 2896 (27.2) | 1212 (28.4) | 6293 (23.2) | |
| 2 | 3039 (6.3) | 825 (7.7) | 387 (9.1) | 1964 (7.3) | |
| 3 | 1386 (2.9) | 343 (3.2) | 170 (4.0) | 1113 (4.1) | |
| **TNM stage** | | | | | |
| I | 22834 (47.4) | 4579 (43.0) | 1428 (33.5) | 10337 (38.2) | < 0.001 |
| II | 20390 (42.3) | 4688 (44.0) | 2167 (50.8) | 13119 (48.5) | |
| III | 4986 (10.3) | 1389 (13.0) | 674 (15.8) | 3620 (13.4) | |
| **Histologic grade** | | | | | |
| 1 | 1 | 4 | 1 | 6 | |

(Continued)
Table 2–1. (Continued)

| Characteristics                      | ER+/PR+(n = 50367) | ER+/PR–(n = 11078) | ER–/PR–(n = 4372) | ER–/PR–(n = 27327) | p-value |
|---------------------------------------|--------------------|--------------------|-------------------|--------------------|---------|
| **IDC group**                         |                    |                    |                   |                    |         |
| G1                                    | 10899 (24.8)       | 1600 (16.6)        | 433 (12.2)        | 955 (4.0)          | < 0.001 |
| G2                                    | 23446 (53.4)       | 4967 (51.6)        | 1473 (41.4)       | 6939 (29.1)        |         |
| G3                                    | 9555 (21.8)        | 3063 (31.8)        | 1652 (46.4)       | 15912 (66.8)       |         |
| Unknown                               | 4311               | 1030               | 712               | 3276               |         |
| **Nuclear grade**                     |                    |                    |                   |                    |         |
| G1                                    | 5470 (14.1)        | 957 (11.5)         | 317 (11.2)        | 1165 (5.6)         | < 0.001 |
| G2                                    | 23664 (61.1)       | 4420 (53.0)        | 1190 (42.1)       | 5427 (26.0)        |         |
| G3                                    | 9603 (24.8)        | 2959 (35.5)        | 1319 (46.7)       | 14298 (68.4)       |         |
| Unknown                               | 9474               | 2324               | 1444              | 6192               |         |
| **LVI**                               |                    |                    |                   |                    |         |
| Negative                              | 28007 (68.2)       | 5969 (68.4)        | 1838 (61.1)       | 15188 (69.6)       | < 0.001 |
| Positive                              | 13041 (31.8)       | 2760 (31.6)        | 1169 (38.9)       | 6633 (30.4)        |         |
| Unknown                               | 7163               | 1931               | 1263              | 5261               |         |
| **HER2**                              |                    |                    |                   |                    |         |
| Negative                              | 38804 (87.4)       | 7454 (77.4)        | 2587 (73.3)       | 15702 (64.8)       | < 0.001 |
| Positive                              | 5618 (12.6)        | 2174 (22.6)        | 941 (26.7)        | 8547 (35.2)        |         |
| Unknown                               | 3789               | 1032               | 742               | 2833               |         |
| **Ki67**                              |                    |                    |                   |                    |         |
| ≤ 20                                  | 17426 (73.6)       | 2976 (67.0)        | 672 (50.7)        | 4553 (37.3)        | < 0.001 |
| > 20                                  | 6240 (26.4)        | 1467 (33.0)        | 653 (49.3)        | 7653 (62.7)        |         |
| Unknown                               | 24545              | 6217               | 2945              | 14876              |         |
| **Chemotherapy**                      |                    |                    |                   |                    |         |
| No                                    | 14666 (33.5)       | 2862 (30.1)        | 585 (15.5)        | 3077 (12.5)        | < 0.001 |
| Yes                                   | 29175 (66.5)       | 6638 (69.9)        | 3184 (84.5)       | 21541 (87.5)       |         |
| Unknown                               | 4368               | 1160               | 501               | 2464               |         |
| **Radiation therapy**                 |                    |                    |                   |                    |         |
| No                                    | 14918 (35.1)       | 3746 (40.8)        | 1531 (43.8)       | 9606 (41.1)        | < 0.001 |
| Yes                                   | 27550 (64.9)       | 5425 (59.2)        | 1965 (56.2)       | 13791 (58.9)       |         |
| Unknown                               | 5743               | 1489               | 774               | 3685               |         |
| **Hormonal therapy**                  |                    |                    |                   |                    |         |
| No                                    | 2451 (5.8)         | 761 (8.4)          | 515 (15.3)        | 19317 (87.0)       | < 0.001 |
| Yes                                   | 39500 (94.2)       | 8297 (91.6)        | 2851 (84.7)       | 2887 (13.0)        |         |
| Unknown                               | 6260               | 1602               | 904               | 4878               |         |
| **Surgery**                           |                    |                    |                   |                    |         |
| TM                                    | 20590 (43.2)       | 5482 (52.1)        | 2392 (57.0)       | 14235 (53.2)       | < 0.001 |
| BCS                                   | 27017 (56.8)       | 5044 (47.9)        | 1805 (43.0)       | 12547 (46.8)       |         |
| Unknown                               | 604                | 134                | 73                | 300                |         |
| **Axillary op**                       |                    |                    |                   |                    |         |
| SNB                                   | 14612 (30.6)       | 2651 (25.1)        | 518 (12.3)        | 6308 (23.5)        | < 0.001 |
| ALND                                  | 30889 (64.7)       | 7444 (70.5)        | 3491 (82.8)       | 19288 (71.9)       |         |
| No op                                 | 2210 (4.6)         | 462 (4.4)          | 205 (4.9)         | 1243 (4.6)         |         |
| Unknown                               | 500                | 103                | 56                | 243                |         |

ALND, axillary lymph node dissection; BCS, breast conserving surgery; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; LVI, lymphovascular invasion; PR, progesterone receptor; SNB, sentinel node biopsy; TM, total mastectomy.

[Link to publication]

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| Characteristics  | ER+/PR+(n = 50367) | ER+/PR−(n = 11078) | ER−/PR+(n = 4372) | ER−/PR−(n = 27327) | p-value |
|-----------------|------------------|------------------|------------------|------------------|--------|
| Age at operation|                  |                  |                  |                  |        |
| ≤ 40            | 228 (10.6)       | 23 (5.5)         | 17 (16.7)        | 28 (11.4)        | 0.001  |
| ≥ 41            | 1928 (89.4)      | 395 (94.5)       | 85 (83.3)        | 217 (88.6)       |        |
| T stage         |                  |                  |                  |                  |        |
| 0               | 1 (< 0.1)        | 0 (< 0.1)        | 0 (< 0.1)        | 0 (< 0.1)        | 0.010  |
| 1               | 1066 (49.4)      | 204 (48.8)       | 42 (41.2)        | 99 (40.4)        |        |
| 2               | 893 (41.4)       | 158 (37.8)       | 51 (50.0)        | 115 (46.9)       |        |
| 3               | 186 (8.6)        | 48 (11.5)        | 9 (8.8)          | 28 (11.4)        |        |
| 4               | 10 (0.5)         | 8 (1.9)          | 0 (< 0.1)        | 3 (1.2)          |        |
| N stage         |                  |                  |                  |                  |        |
| 0               | 1418 (65.8)      | 281 (67.2)       | 55 (53.9)        | 146 (59.6)       | < 0.001|
| 1               | 533 (24.7)       | 83 (19.9)        | 29 (28.4)        | 54 (22.0)        |        |
| 2               | 129 (6.0)        | 37 (8.9)         | 12 (11.8)        | 29 (11.8)        |        |
| 3               | 76 (3.5)         | 17 (4.1)         | 6 (5.9)          | 16 (6.5)         |        |
| TNM stage       |                  |                  |                  |                  |        |
| I               | 859 (39.8)       | 173 (41.4)       | 29 (28.4)        | 77 (31.4)        | < 0.001|
| II              | 1022 (47.4)      | 171 (40.9)       | 53 (52.0)        | 111 (45.3)       |        |
| III             | 275 (12.8)       | 74 (17.7)        | 20 (19.6)        | 57 (23.3)        |        |
| Histologic grade|                  |                  |                  |                  |        |
| G1              | 386 (26.8)       | 52 (20.3)        | 11 (21.6)        | 16 (12.5)        | < 0.001|
| G2              | 893 (62.0)       | 173 (67.6)       | 30 (58.8)        | 67 (52.3)        |        |
| G3              | 161 (11.2)       | 31 (12.1)        | 10 (19.6)        | 45 (35.2)        |        |
| Unknown         | 716              | 162              | 51               | 117              |        |
| Nuclear grade   |                  |                  |                  |                  |        |
| G1              | 376 (26.1)       | 55 (20.9)        | 13 (27.7)        | 15 (11.6)        | < 0.001|
| G2              | 901 (62.5)       | 171 (65.0)       | 30 (63.8)        | 66 (51.2)        |        |
| G3              | 165 (11.4)       | 37 (14.1)        | 4 (8.5)          | 48 (37.2)        |        |
| Unknown         | 714              | 155              | 55               | 116              |        |
| LVI             |                  |                  |                  |                  |        |
| Negative        | 1560 (83.7)      | 289 (82.3)       | 60 (82.2)        | 136 (69.7)       | < 0.001|
| Positive        | 303 (16.3)       | 62 (17.7)        | 13 (17.8)        | 59 (30.3)        |        |
| Unknown         | 293              | 67               | 29               | 50               |        |
| HER2            |                  |                  |                  |                  |        |
| Negative        | 1909 (95.3)      | 354 (93.7)       | 87 (95.6)        | 166 (79.8)       | < 0.001|
| Positive        | 94 (4.7)         | 24 (6.3)         | 4 (4.4)          | 42 (20.2)        |        |
| Unknown         | 153              | 40               | 11               | 37               |        |
| Ki67            |                  |                  |                  |                  |        |
| ≤ 20            | 943 (86.4)       | 182 (91.0)       | 22 (88.0)        | 71 (69.6)        | < 0.001|
| > 20            | 149 (13.6)       | 18 (9.0)         | 3 (12.0)         | 31 (30.4)        |        |
| Unknown         | 1064             | 218              | 77               | 143              |        |
| Chemotherapy    |                  |                  |                  |                  |        |
| No              | 606 (30.4)       | 129 (34.1)       | 17 (18.1)        | 32 (14.2)        | < 0.001|
| Yes             | 1386 (69.6)      | 249 (65.9)       | 77 (81.9)        | 194 (85.8)       |        |
| Unknown         | 164              | 40               | 8                | 19               |        |
| Radiation therapy|                 |                  |                  |                  |        |
| No              | 775 (40.1)       | 137 (37.5)       | 36 (40.0)        | 94 (44.1)        | 0.486  |

(Continued)
ER−/PR+ status conferred the highest risk on OS (HR: 1.771, 95% CI: 1.088–2.884; p = 0.022), followed by ER+/PR− status (HR: 1.673, 95% CI: 1.182–2.367; p = 0.004), ER−/PR− status (HR: 1.574, 95% CI: 1.032–2.400; p = 0.035), and ER+/PR+ status (reference).

**Comparison of survival between IDC and ILC in each hormone receptor expression subgroup**

We compared survival between the IDC and ILC populations in each hormone expression subgroup. There were no differences in survival between the IDC and ILC populations in the...
Fig 2. Kaplan–Meier survival analysis of overall survival (OS) (A) and breast cancer-specific survival (BCSS) (B) according to estrogen receptor and progesterone receptor status.

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Fig 3. Kaplan–Meier survival analysis of overall survival (OS) (A, C) and breast cancer-specific survival (BCSS) (B, D) in the invasive ductal carcinoma (A, B) and invasive lobular carcinoma groups (C, D).

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ER+/PR+ subgroup (5-year OS in IDC group: 88.9% vs. ILC group: 88.0%; p = 0.859; 5-year BCSS in IDC group: 96.1% vs. ILC group: 95.6%; p = 0.828). There were similar results in the ER+/PR− subgroup (5-year OS in IDC group: 83.0% vs. ILC group: 80.3%; p = 0.438; 5-year BCSS in IDC group: 93.2% vs. ILC group: 90.1%; p = 0.053) and the ER−/PR− subgroup (5-year OS in IDC group: 83.4% vs. ILC group: 82.2%; p = 0.522; 5-year BCSS in IDC group: 91.8% vs. ILC group: 88.8%; p = 0.291). However, the ER−/PR− subgroup showed differences in survival between the IDC and ILC populations (5-year OS in IDC group: 81.9% vs. ILC group: 74.4%; p = 0.040; 5-year BCSS in IDC group: 92.0% vs. ILC group: 87.1%; p = 0.049). In the univariate Cox regression analysis, the HR of ILC in the ER−/PR− subgroup was 1.345 (95% CI: 1.012–1.788; p = 0.041).

Discussion

In the present study, we compared the clinicopathological characteristics and survival outcomes of invasive breast cancer cases in Korea. In Asia, fewer studies than in the West have compared clinicopathological characteristics and survival between ILC and IDC cases of different molecular subtypes. According to a study using the SEER database, compared to patients with IDC, patients with ILC are older at diagnosis, have larger tumor size, show more advanced stage, have lower histological grade, and display more hormone expression positivity [6]. We found similar clinicopathological tendencies in the KBCR database. Several studies have asserted that ILC cases show larger tumor size and more advanced stage than IDC cases because the indistinct tumor growth pattern leads to delays in diagnosis and detection failure [16–19]. In the present study, total mastectomy was more common in patients with ILC than in those with IDC, as in other studies, probably because of the larger tumor size, more advanced stage, and multifocal tendency. For the comparison of survival between ILC and IDC cases, several studies have been carried out with conflicting results. In a study by Chen et al., ILC cases showed better OS before 60 months (HR of IDC vs. ILC: 1.118; p < 0.0001); thereafter, IDC cases showed better OS (HR of IDC vs. ILC: 0.775; p < 0.0001). The disease-specific survival curve showed that IDC cases had better survival outcomes than ILC cases did (HR of IDC vs. ILC: 0.809; p < 0.0001) [6]. In other reports, ILC cases had similar or better survival outcomes compared to those of IDC cases [8–14]. In the present study, there were no meaningful differences in OS or BCSS between patients with ILC and IDC in the KBCR database.

Breast cancer is a heterogeneous disease with varying hormone receptor status, and each subtype has different clinical features, treatment options, outcomes, and prognoses. For this
reason, the hormone receptor subtypes are being studied worldwide. The ER+/PR+ subgroup presented the best survival in the present study, while the ER−/PR− subgroup presented the worst when the total study population was compared according to hormone expression status. The HR of ER+/PR− expression on OS was 1.419 (95% CI: 1.331–1.513; p < 0.001), while that of ER−/PR+ expression was 1.344 (95% CI: 1.237–1.459; p < 0.001) and that of ER−/PR− expression was 1.620 (95% CI: 1.528–1.718; p < 0.001) when ER+/PR+ expression was used as a reference. The HR of ER+/PR− expression on BCSS was 1.516 (95% CI: 1.364–1.685; p < 0.001), while that of ER−/PR+ expression was 1.625 (95% CI: 1.435–1.841; p < 0.001) and that of ER−/PR− expression was 1.915 (95% CI: 1.747–2.098; p < 0.001) when ER+/PR+ expression was used as a reference.

In the IDC group, the order of survival HR was similar to that in the total population. In contrast, the ILC group showed a slightly different order of survival HR. The HR of ER+/PR− expression on OS was 1.673 (95% CI: 1.182–2.367; p = 0.004), while that of ER−/PR+ expression was 1.771 (95% CI: 1.088–2.884; p < 0.022) and that of ER−/PR− expression was 1.574 (95% CI: 1.032–2.400; p < 0.035) when ER+/PR+ expression was used as a reference. The HR of ER+/PR− expression on BCSS was 2.389 (95% CI: 1.422–4.016; p = 0.001), while that of ER−/PR+ expression was 2.629 (95% CI: 1.322–5.228; p = 0.006) when ER+/PR+ expression was used as a reference.

When analyzing each hormone receptor expression subgroup, as shown in Fig 5, there were no significant differences in survival between the IDC and ILC populations. However, the ER−/PR− subgroup showed differences in survival between the IDC and ILC populations (5-year OS in IDC group: 87.8% vs. ILC group: 87.5%; p = 0.040; 5-year BCSS in IDC group: 92.0% vs. ILC group: 87.1%; p = 0.049). In some studies, hormone receptor negativity was shown to reduce survival rates in the ILC group. In a study by Francesca et al., triple negative ILC showed the worst survival outcomes (79.7% at 5-years and 73.8% at 10-years) among all histological types. The same study reported that triple negative ILC showed a higher metastatic lymph node ratio (> 0.65) and lower response to chemotherapy than those of other triple negative breast cancer histological types [20]. It is hard to predict outcomes based on current classification and treatment regimens because the ER−/PR− population shows heterogeneity. Therefore, researchers must identify new molecular targets and subtypes. Understanding the heterogeneous molecular subtypes will allow targeted treatments in the future.

There were some limitations to this study. First, it was retrospective, so selection bias may have been present. However, the incidence of ILC is too small to study prospectively. Second, some data were clearly missing during the follow-up period, but we reasoned that the data were valuable and reliable because they were sourced from a large-scale database of one country with long-term follow-up and they corroborated findings of previous studies. Moreover, hormone receptor expression of 1–10% of tumor nuclei positivity was considered as negative, because it was initially registered as negative when the database started to be built. Another limitation may be that the neoadjuvant chemotherapy is not isolated, but in Korea, since it started in the 2010s, the number of patients who received neoadjuvant chemotherapy is small, so it will not have a significant effect.

In conclusion, we reviewed the clinicopathological characteristics and survival outcomes of invasive breast cancer cases in Korea. There was no difference in survival outcomes between ILC and IDC cases in the present study. However, in the ER−/PR− subgroup, the survival outcomes of ILC cases were worse than those of IDC cases. Given that the ER−/PR− group was heterogeneous and the incidence of ILC was low, further large studies are needed to allow comprehensive classification and identification of treatment regimens.
Fig 5. Kaplan–Meier survival analysis of overall survival (OS) (A, C, E, G) and breast cancer-specific survival (BCSS) (B, D, F, H), in the ER positive/PR positive (A, B), ER positive/PR negative (C, D), ER negative/PR positive (E, F), and ER negative/PR negative subgroups (G, H).

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Supporting information

S1 Table. Inclusion/Exclusion criteria for patient selection.

(DOCX)

S1 Data.

(XLSX)

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References

1. Ahn SH, Yoo KY; Korean Breast Cancer Society. Chronological changes of clinical characteristics in 31,115 new breast cancer patients among Koreans during 1996–2004. Breast Cancer Res Treat 2006; 99:209–14. https://doi.org/10.1007/s10549-006-9188-x PMID: 16862450

2. Ko SS; Korean Breast Cancer Society. Chronological changing patterns of clinical characteristics of Korean breast cancer patients during 10 years (1996–2006) using nationwide breast cancer registration on-line program: biannual update. J Surg Oncol 2008; 98:318–23. https://doi.org/10.1002/jso.21110 PMID: 18623175

3. Ko BS, Noh WC, Kang SS, Park BW, Kang EY, Paik NS, et al. Changing patterns in the clinical characteristics of Korean breast cancer from 1996–2010 using an online nationwide breast cancer database. J Breast Cancer. 2012 Dec; 15(4):393–400. https://doi.org/10.4048/jbc.2012.15.4.393 PMID: 23346167

4. Son BH, Kwak BS, Kim JK, Kim HJ, Hong SJ, Lee JS, et al. Changing patterns in the clinical characteristics of Korean patients with breast cancer during the last 15 years. Arch Surg. 2006 Feb; 141(2):155–60. https://doi.org/10.1001/archsurg.141.2.155 PMID: 16490892

5. Kang SY, Kim YS, Kim Z, Kim HY, Kim HJ, Park S, et al. Breast Cancer Statistics in Korea in 2017: Data from a Breast Cancer Registry. J Breast Cancer. 2020 Apr 7; 23(2):115–128. https://doi.org/10.4048/jbc.2020.23.e24 PMID: 32395372

6. Chen Z, Yang J, Li S, Lv M, Shen Y, Wang B, et al. Invasive lobular carcinoma of the breast: A special histological type compared with invasive ductal carcinoma. PLoS One. 2017 Sep 1; 12(9):e0182397. https://doi.org/10.1371/journal.pone.0182397 PMID: 28863134

7. Yang M, Bao W, Zhang X, Kang Y, Haffty B, Zhang L. Short-term and long-term clinical outcomes of uncommon types of invasive breast cancer. Histopathology. 2017 Dec; 71(6):874–886. https://doi.org/10.1111/his.13328 PMID: 28746732

8. Zhao H. The prognosis of invasive ductal carcinoma, lobular carcinoma and mixed ductal and lobular carcinoma according to molecular subtypes of the breast. Breast Cancer. 2021 Jan; 28(1):187–195. https://doi.org/10.1007/s12282-020-01146-4 PMID: 32812198

9. Duraker N, Hot S, Akan A, Nayır PÖ. A Comparison of the Clinicopathological Features, Metastasis Sites and Survival Outcomes of Invasive Lobular, Invasive Ductal and Mixed Invasive Ductal and Lobular Breast Carcinoma. Eur J Breast Health. 2020 Jan 1; 16(1):22–31. https://doi.org/10.5152/ejbh.2019.5004 PMID: 31912010

10. Wasif N, Maggard MA, Ko CY, Giuliano AE. Invasive lobular vs. ductal breast cancer: a stage-matched comparison of outcomes. Ann Surg Oncol. 2010 Jul; 17(7):1862–9. https://doi.org/10.1245/s10434-010-0953-z PMID: 20162457

11. Sastrre-Garau X, Jouve M, Asselan B, Vincent-Salomon A, Beuzeboc P, Dorval T, et al. Infiltrating lobular carcinoma of the breast. Clinicopathologic analysis of 975 cases with reference to data on conservative therapy and metastatic patterns. Cancer. 1996 Jan 1; 77(1):113–20. https://doi.org/10.1002/(SICI) 1097-0424(19960101)77:1<113::AID-ONC219>3.0.CO;2-8 PMID: 8639816

12. Peiro G, Bornstein BA, Connolly JL, Gelman R, Hetelekidis S, Nixon AJ, et al. The influence of infiltrating lobular carcinoma on the outcome of patients treated with breast-conserving surgery and radiation
13. Park JS, Choi DH, Huh SJ, Park W, Kim YI, Nam SJ, et al. Comparison of Clinicopathological Features and Treatment Results between Invasive Lobular Carcinoma and Ductal Carcinoma of the Breast. J Breast Cancer. 2015 Sep; 18(3):285–90. https://doi.org/10.4048/jbc.2015.18.3.285 PMID: 26472980

14. Lim ST, Yu JH, Park HK, Moon BI, Ko BK, Suh YJ. A comparison of the clinical outcomes of patients with invasive lobular carcinoma and invasive ductal carcinoma of the breast according to molecular subtype in a Korean population. World J Surg Oncol. 2014 Mar 13; 12:56. https://doi.org/10.1186/1477-7819-12-56 PMID: 24621330

15. Lee SB, Sohn G, Kim J, Chung IY, Kim HJ, Ko BS, et al. Chronological Improvement in Survival of Patients with Breast Cancer: A Large-Scale, Single-Center Study. J Breast Cancer. 2018 Mar; 21(1):70–79. https://doi.org/10.4048/jbc.2018.21.1.70 PMID: 29628986

16. Yeatman TJ, Cantor AB, Smith TJ, Smith SK, Reintgen DS, Miller MS, et al. Tumor biology of infiltrating lobular carcinoma. Implications for management. Ann Surg. 1995 Oct; 222(4):549–59; discussion 559–61. https://doi.org/10.1097/0000658-199522240-00012 PMID: 7574934

17. Uchiyama N, Miyakawa K, Moriyama N, Kumazaki T. Radiographic features of invasive lobular carcinoma of the breast. Radiat Med. 2001 Jan-Feb; 19(1):19–25. PMID: 11305614

18. Boetes C, Veltman J, van Die L, Bult P, Wobbes T, Barentsz JO. The role of MRI in invasive lobular carcinoma. Breast Cancer Res Treat. 2004 Jul; 86(1):31–7. https://doi.org/10.1023/B:BREA.0000032921.10481.de PMID: 15218359

19. Veltman J, Boetes C, van Die L, Bult P, Blickman JG, Barentsz JO. Mammographic detection and staging of invasive lobular carcinoma. Clin Imaging. 2006 Mar-Apr; 30(2):94–8. https://doi.org/10.1016/j.clim.2005.09.021 PMID: 16500539

20. Sanges F, Floris M, Cossu-Rocca P, Muroni MR, Pira G, Urru SAM, et al. Histologic subtyping affecting outcome of triple negative breast cancer: a large Sardinian population-based analysis. BMC Cancer. 2020 Jun 2; 20(1):491. https://doi.org/10.1186/s12885-020-06998-9 PMID: 32487046