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Long-Term Survival in a Large Spanish Breast Cancer Cohort: Age-Stratified Outcomes from the Institut Català d'Oncologia (2010-2014) Observational Study

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ABSTRACT

Large, consistently treated breast cancer (BC) cohorts with extended monitoring remain uncommon for evaluating long-term outcomes. The Institut Català d'Oncologia (ICO) Breast Cancer Cohort was established to describe real-world treatment tendencies and 5- and 10-year overall survival, emphasizing patients younger than 40 and those aged 70 or above—groups often lacking representation in trials. This retrospective observational analysis included all individuals with histologically verified invasive BC diagnosed and treated at ICO, Spain, from 2010 to 2014, with outcome tracking until November 2023. Detailed demographic, pathologic, and therapeutic information was extracted. Overall survival (OS) was estimated through Kaplan-Meier analysis and stratified by prognostic indicators across three age brackets: ≤40, 41-69, and ≥70 years. Mortality risks were assessed with a multivariate Cox proportional hazards model controlling for tumor subtype, disease stage, and histological grade. Among 3451 women with stage I-IV BC, the average age was 58 years (range 19-98). Of these, 371 (10.8%) were ≤40 and 756 (21.9%) were ≥70. After an average 9.9-year follow-up (SD = 3.5), 5- and 10-year OS were 89% (95% CI 86-92%) and 85% (95% CI 81-88%) for patients ≤40; 91% (95% CI 90-92%) and 85% (95% CI 83-86%) for ages 41-69; and 70% (95% CI 66-73%) and 50% (95% CI 47-54%) for those ≥70. Relative survival (RS) at 5 and 10 years reached 92% and 88% for patients younger than 70, and 82% and 77% for those aged 70 or older. In the Cox model, being ≥70 years was linked to a hazard ratio (HR) of 4.90 (95% CI 3.44-6.97; $p < 0.001$) versus the 41-69 group. The ICO Breast Cancer Cohort—currently the largest Spanish dataset with long-term follow-up—demonstrates that both age and tumor subtype play decisive roles in shaping survival outcomes in breast cancer.

Keywords: Observational cohort, Breast cancer, Long-term data, Survival, Real-world analysis, Follow-up

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Introduction

Because breast cancer exhibits marked biological diversity, precision medicine seeks to refine outcome prediction and guide tailored therapy. Longitudinal datasets are essential for identifying these variations. Compared to the abundance of prospective etiological studies, only a few large retrospective cohorts offer extended survival follow-up [1-3]. Age is often an overlooked determinant, yet the most unfavorable outcomes frequently occur in the youngest and oldest patients [4, 5].

Among women under 40 years, BC remains the principal cause of cancer-related mortality. This group often faces delayed diagnosis due to limited screening access and symptomatic presentation at advanced stages. Evidence also indicates age-specific biological differences: younger women more commonly develop aggressive subtypes such as triple-negative (TNBC) and HER2-positive (HER2+) cancers [6, 7]. Even within hormone receptor-positive (HR+) disease, tumors are frequently higher grade, and mortality risk is roughly 1.5-2 times higher than in women over 40 [4, 5, 8-10].

As populations age, the number of BC diagnoses in those over 70 years is expected to rise [9]. Despite a lower frequency of aggressive subtypes, survival outcomes in older patients vary widely. Those presenting with locally

advanced or metastatic disease generally fare worse, and advanced age independently predicts early mortality. Many elderly patients also receive reduced-intensity or non-standard regimens due to frailty, comorbid conditions, or anticipated toxicity [4, 11-13].

To address the lack of large, long-term datasets, the Institut Català d'Oncologia (ICO)—a national cancer reference center in Spain—created a comprehensive BC registry. ICO integrates prevention, diagnostics, treatment, patient follow-up, education, and translational and clinical research. The network encompasses three main institutions—Hospital Universitari de Bellvitge (HUB, L'Hospitalet, Barcelona), Hospital Universitari Doctor Josep Trueta (HUDJT, Girona), and Hospital Universitari Germans Trias i Pujol (HUGTiP, Badalona)—and collaborates with 20 regional hospitals, providing care for about 3 million residents in Catalonia. This project aimed to compile robust, real-world data from patients treated at ICO between 2010 and 2014 to produce high-quality evidence on long-term outcomes.

The study hypothesizes that BC patients at age extremes (<40 and ≥70 years) experience poorer survival than those of intermediate age. The objectives were to analyze overall survival (OS) in these age strata and to examine the interaction of age with tumor subtype, clinical stage, and histologic grade within a large, long-term institutional cohort.

Materials and Methods

Study population and data acquisition

This multi-institutional cohort, developed under the coordination of the Institut Català d'Oncologia (ICO), was designed to calculate and publish overall survival (OS) indicators as measures of outcome and institutional quality, in accordance with the ESMO GROW reporting framework for real-world oncology data [14].

The observation window extended from 1 January 2010 to 31 December 2014, including all women treated in any of the three ICO hospitals, with continued follow-up through 30 November 2023.

Eligible participants were female patients aged 18 years or older, diagnosed with invasive breast carcinoma (all molecular subtypes), with documented stage at presentation, and who underwent care at an ICO center or one of its partner hospitals within the regional network. This included individuals receiving surgery or systemic therapy—either at ICO or collaborating institutions.

Case identification was based on several institutional data streams:

Histopathology department reports,

Hospital discharge registries, and

The ICO Girona Tumor Registry.

Clinical and demographic data were retrieved from:

Electronic health records across ICO hospitals,

The Shared Clinical History of Catalonia,

The ESPOQ chemotherapy prescription registry, and

The ARIA radiotherapy system.

The ICO Information Systems Division designed and maintained a dedicated study database, where trained abstractors entered data manually under physician oversight.

Variables collected included baseline characteristics, diagnostic and prognostic indices, first-line treatment type (surgery, chemotherapy, endocrine or targeted therapy, and external or internal radiotherapy), treatment response, survival status, and last known follow-up date. Data regarding therapies performed outside ICO were sourced from the treating institution.

The diagnosis date corresponded to the first positive biopsy confirming malignancy. Death data were routinely updated via linkage with the National Death Index (INDEF). When no death was recorded, the most recent follow-up date was determined from the last visit at ICO or another institution, whichever occurred later. The administrative censoring date was set to 30 November 2023.

Ethical clearance for the study was provided by the Research Ethics Committee of Hospital Universitari de Bellvitge (Reference: PR108/24).

Statistical procedures

Cohort characteristics were summarized using absolute counts and proportions for categorical variables and medians with ranges and interquartile intervals (IQRs) for continuous variables.

Survival duration was defined as the interval in years from diagnosis to either death or censoring on 30 November 2023. Overall survival (OS) was calculated using Kaplan-Meier estimation, with median OS and 95% confidence intervals (CIs) reported.

Relative survival (RS) was used to estimate net survival, adjusting for age-, sex-, and calendar year-specific expected mortality rates in the general Spanish population. Calculations were performed using the Pohar-Perme method and the 2023 Human Mortality Database life tables for Spain [15]. RS values were computed at 2, 5, and 10 years.

A multivariate Cox regression model assessed mortality risk by age group, controlling for tumor subtype, disease stage, and histologic grade. Age-covariate interaction terms were retained in the model when the likelihood ratio test reached statistical significance.

Results and Discussion

Of the 4065 identified cases, 3451 patients satisfied the inclusion criteria. The mean age was 58 years (range 19-98). Among them, 371 (10.8%) were aged ≤40, 2324 (67.3%) were 41-69, and 756 (21.9%) were ≥70.

By molecular profile, 2358 (68.3%) were HR+/HER2−, 459 (13.3%) were HER2+, 403 (11.6%) were TNBC, and 231 (6.6%) could not be classified.

Stage distribution was as follows: stage I, 1111 patients (32.2%); stage II, 1593 (46.2%); stage III, 583 (16.9%); and stage IV, 164 (4.8%).

After an average follow-up of 9.9 years (SD = 3.5), the median OS had not been reached. The 5-year OS was 89% (95% CI: 86-92%).

Pathological and clinical patterns by age category

Among the 371 patients (10.8%) diagnosed at age 40 or below, the mean age was 37 years [IQR 33.0-39.0]. Within this younger subset, the most frequent tumor subtype was HR+/HER2− (221 patients, 59.6%), followed by TNBC (73, 19.7%) and HER2+ (61, 16.4%).

Most cases in this group were stage II (58%) or stage III (22.4%) at presentation. Invasive ductal carcinoma accounted for 88.9%, while invasive lobular carcinoma represented 2.2%. Grade III was predominant (44.7%), and Ki67 ≥ 20% was observed in 69.8% **(Table 1)**.

In terms of management, 53.9% underwent primary surgery, while 42.9% received neoadjuvant chemotherapy. Breast-conserving surgery (BCS) was the leading operative technique (51.9%), and 59.5% of patients had axillary dissection **(Table 2)**.

Table 1. Clinicopathological variables by age group.

Characteristic	Overall N = 3451	≤40 years N = 371	41-69 years N = 2324	≥70 years N = 756	p-value
Median age at diagnosis [IQR]	58.0 [47.0; 68.0]	37.0 [33.0; 39.0]	55.0 [48.0; 62.0]	77.0 [73.0; 81.0]	<0.001
Molecular subtype, n (%)					<0.001
HR+/HER2−	2358 (68.3%)	221 (59.6%)	1605 (69.1%)	532 (70.4%)	
HER2+	459 (13.3%)	61 (16.4%)	321 (13.8%)	77 (10.2%)	
Triple-negative	403 (11.7%)	73 (19.7%)	244 (10.5%)	86 (11.4%)	
Unknown	231 (6.7%)	16 (4.3%)	154 (6.6%)	61 (8.1%)	
Tumor stage, n (%)					<0.001
I	1111 (32.2%)	58 (15.6%)	840 (36.1%)	213 (28.2%)	
II	1593 (46.2%)	215 (58.0%)	1030 (44.3%)	348 (46.0%)	
III	583 (16.9%)	83 (22.4%)	369 (15.9%)	131 (17.3%)	
IV	164 (4.8%)	15 (4.0%)	85 (3.7%)	64 (8.5%)	
Histologic type, n (%)					<0.001
Invasive ductal carcinoma	2765 (80.1%)	330 (88.9%)	1894 (81.5%)	541 (71.6%)	
Invasive lobular carcinoma	318 (9.2%)	8 (2.2%)	230 (9.9%)	80 (10.6%)	
Other	297 (8.6%)	29 (7.8%)	169 (7.3%)	99 (13.1%)	
Unknown	71 (2.1%)	4 (1.1%)	31 (1.3%)	36 (4.8%)	
Histologic grade, n (%)					<0.001

Grade I	687 (19.9%)	45 (12.1%)	490 (21.1%)	152 (20.1%)	
Grade II	1358 (39.4%)	120 (32.3%)	956 (41.1%)	282 (37.3%)	
Grade III	965 (28.0%)	166 (44.7%)	600 (25.8%)	199 (26.3%)	
Not documented	441 (12.8%)	40 (10.8%)	278 (12.0%)	123 (16.3%)	
Ki67 proliferation index, n (%)					<0.001
<20%	1135 (32.9%)	61 (16.4%)	810 (34.9%)	264 (34.9%)	
≥20%	1669 (48.4%)	259 (69.8%)	1090 (46.9%)	320 (42.3%)	
Not documented	647 (18.7%)	51 (13.7%)	424 (18.2%)	172 (22.8%)	

Table 2. Distribution of treatment strategies and surgical procedures across age strata.

Characteristic	Overall N = 3451	≤40 years N = 371	41-69 years N = 2324	≥70 years N = 756	p-value
Initial treatment modality, n (%)					<0.001
Surgery	2505 (72.6%)	200 (53.9%)	1760 (75.7%)	545 (72.1%)	
Neoadjuvant therapy	792 (22.9%)	159 (42.9%)	487 (21.0%)	146 (19.3%)	
Palliative intent	124 (3.6%)	11 (3.0%)	64 (2.8%)	49 (6.5%)	
Other	30 (0.9%)	1 (0.3%)	13 (0.6%)	16 (2.1%)	
Surgical procedure type, n (%)					<0.001
Mastectomy	676 (20.5%)	146 (40.3%)	394 (17.4%)	136 (20.0%)	
Breast-conserving surgery	2138 (64.8%)	188 (51.9%)	1540 (68.2%)	410 (60.2%)	
Not documented	487 (14.8%)	28 (7.7%)	324 (14.3%)	135 (19.8%)	
Sentinel lymph node biopsy performed, n (%)	2165 (67.7%)	210 (60.2%)	1626 (74.3%)	329 (49.8%)	<0.001
Positive sentinel node, n (%)	728 (33.6%)	95 (45.2%)	537 (33.2%)	96 (28.2%)	<0.001
Type of sentinel node metastasis, n (%)					0.247
Micrometastasis (pN1mi)	340 (50.9%)	52 (59.1%)	243 (49.9%)	45 (48.4%)	
Macrometastasis (pN1a)	328 (49.1%)	36 (40.9%)	244 (50.1%)	48 (51.6%)	
Axillary lymphadenectomy, n (%)	1310 (43.0%)	195 (59.5%)	861 (41.6%)	254 (39.2%)	<0.001
Adjuvant chemotherapy, n (%)	1233 (35.7%)	157 (42.3%)	966 (41.6%)	110 (14.6%)	<0.001
Trastuzumab administration[1], n (%)	446 (36.2%)	72 (45.9%)	322 (33.3%)	52 (47.2%)	<0.001
Vital status[2], n (%)					<0.001
Deceased	891 (25.8%)	61 (16.4%)	408 (17.6%)	422 (55.8%)	
Alive	2560 (74.2%)	310 (83.6%)	1916 (82.4%)	334 (44.2%)	
Follow-up duration (years), Mean (SD)	9.9 (3.5)	10.5 (3.2)	10.5 (3.0)	8.0 (4.2)	

[1] Percentages are calculated among patients receiving adjuvant therapy.

[2] Administrative censoring date: 30 November 2023.

For individuals aged 41-69 years (n = 2324; 67.3%), the average age at diagnosis was 55 years [IQR 48.0-62.0]. The HR+/HER2− phenotype accounted for the majority (69.1%), with HER2+ (13.8%) and TNBC (10.5%) following. The bulk of cases were detected at stage II (44.3%) and stage I (36.1%).

Invasive ductal carcinoma predominated (81.5%), and grade II was the most frequent (41.1%), followed by grade I (21.1%). Ki67 ≥ 20% appeared in 46.9% of specimens **(Table 1)**.

Surgery was the initial management for 75.7% of these patients, while 21% underwent neoadjuvant treatment. Breast-conserving procedures (BCS) were employed in 68.2%, and 41.6% received axillary dissection **(Table 2)**.

In the cohort aged 70 years or older (756; 21.9%), the mean age was 77 years [IQR 73.0-81.0]. Here, the HR+/HER2− subtype remained predominant (70.4%), followed by TNBC (11.4%) and HER2+ (10.2%).

Most cases were diagnosed at stage II (46%) and stage I (28.2%), with 8.5% presenting with de novo metastatic disease (stage IV). Invasive ductal histology occurred in 71.6%, while grade II (37.3%) and grade I (20.1%) were the most common. Tumors with Ki67 ≥ 20% comprised 42.3% **(Table 1)**.

Within this age group, surgical intervention was performed first in 72.1%, while neoadjuvant therapy was used in 19.3%. BCS was chosen in 60.2%, and axillary clearance was conducted in 39.2% **(Table 2)**.

Clinicopathological characteristics by breast cancer subtype

In the HR+/HER2− category, the mean age at diagnosis was 58 years [range 19-98]; in HER2+, 54 years [range 22-95]; and in TNBC, 56 years [range 27-97].

Across all molecular profiles, stages I and II predominated, while HER2+ and TNBC presented more frequently in advanced stages (III-IV).

Invasive ductal carcinoma represented 80.1% of tumors, and invasive lobular type appeared in 9.2%. Grade I lesions were more common in HR+/HER2− (25.9%), whereas HER2+ (3.9%) and TNBC (3.5%) rarely exhibited low-grade lesions.

TNBC showed a particularly aggressive profile—70.7% grade III and 75.2% with Ki67 ≥ 20%.

BCS was executed in 66.6% of HR+/HER2−, 65.5% of TNBC, and 56.7% of HER2+ cases. In contrast, mastectomy was used in 29.6% of HER2+, 19.5% of HR+/HER2−, and 19.2% of TNBC patients.

SLNB was the dominant axillary staging technique, though lymphadenectomy was more common in HER2+ (56.8%), TNBC (49.3%), and less so in HR+/HER2− (39.7%).

Primary surgery was applied in 79.3% of HR+/HER2− tumors, compared with 54.2% in HER2+ and 51.9% in TNBC. Conversely, neoadjuvant treatment was given to 42.2% of TNBC, 39.9% of HER2+, and 17.3% of HR+/HER2− individuals.

Clinicopathological characteristics by stage

The mean diagnostic age was comparable among stages: 59 years in stage I [range 27-93], 56 years in stage II [range 19-97], 56 years in stage III [range 25-96], and 63 years in stage IV [range 32-98].

Lumpectomy was carried out in 77.4% of stage I and 66.1% of stage II patients. In stage III, mastectomy was performed in 47.4% of cases.

Among stage IV individuals (n = 164), 31 underwent mastectomy and 17 underwent lumpectomy, totaling 29.2% of that subgroup.

SLNB was used in 90.4% of stage I and 69.3% of stage II patients, but dropped to 23.9% in stage III. Axillary dissection peaked at 93.2% in stage III, compared with 5.4% in stage I.

Overall survival and prognostic factors

Age-stratified overall survival (OS) revealed the following outcomes:

≤40 years: 5-year OS 89% (95% CI 86-92%); 10-year OS 85% (95% CI 81-88%)

41-69 years: 5-year OS 91% (95% CI 90-92%); 10-year OS 85% (95% CI 83-86%)

≥70 years: 5-year OS 70% (95% CI 66-73%); 10-year OS 50% (95% CI 47-54%) **(Figure 1)**

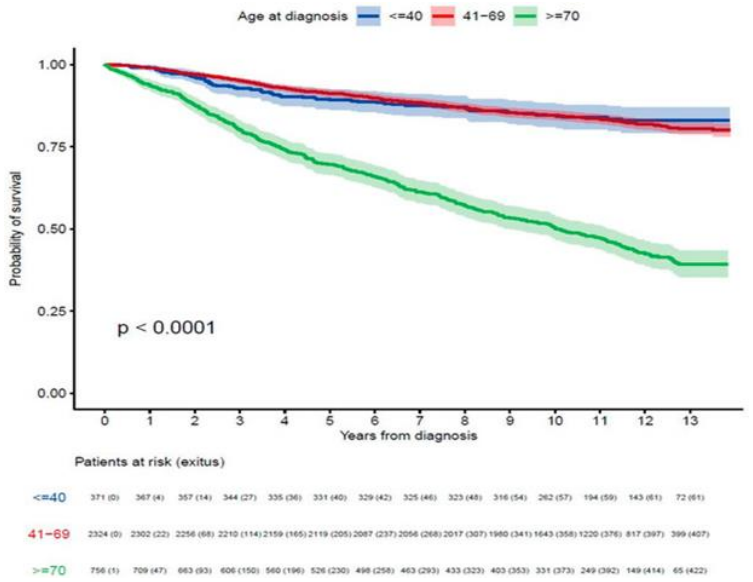

Figure 1. Overall survival probability by age categories.

Among ≤40-year patients, median OS was not attained for stages I-III, but measured 3.7 years (95% CI 2.3-NR) in stage IV.

For those aged 41-69, the median OS also remained unreached for stages I-III, while stage IV yielded 3.5 years (95% CI 3.1-4.2).

In the ≥70 group, median OS was 11 years in stage II, 7.5 years in stage III, and 2 years in stage IV. Only this cohort reached a significant median OS of 10 years (95% CI 8.9-11, $p < 0.0001$), unlike younger counterparts. Five- and ten-year OS values by stage are summarized in **Table 3**, **Figure 2**.

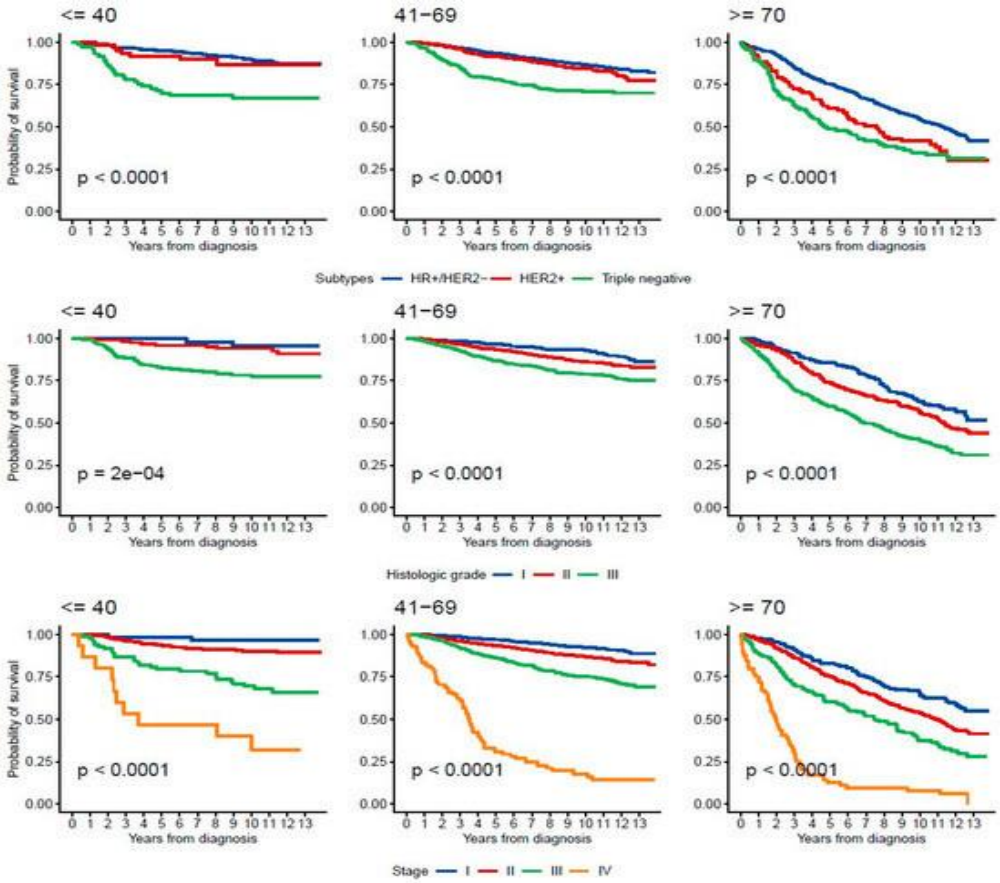

Figure 2. Overall survival patterns stratified by age, tumor grade, and disease stage.

Table 3. Five- and ten-year overall survival rates based on prognostic variables and patient age categories.

	Total		≤40		41-69		≥70	
	5-Year	**10-Year**	**5-Year**	**10-Year**	**5-Year**	**10-Year**	**5-Year**	**10-Year**
Global	86% (85%, 87%)	77% (76%, 78%)	89% (86%, 92%)	85% (81%, 88%)	91% (90%, 92%)	85% (83%, 86%)	70% (66%, 73%)	50% (47%, 54%)
Histologic grade								
I	94 (93, 96)	86 (84, 89)	100 (100, 100)	96 (90, 100)	97 (95, 98)	93 (91, 95)	86 (80, 91)	63 (56, 71)
II	90 (88, 91)	81 (79, 83)	96 (92, 99)	94 (90, 98)	93 (92, 95)	86 (84, 88)	74 (69, 79)	57 (51, 63)
III	80 (78, 83)	71 (68, 74)	83 (77, 89)	78 (72, 85)	87 (84, 89)	79 (76, 82)	60 (53, 67)	40 (34, 48)
Not documented	76 (72, 80)	65 (61, 70)	85 (75, 97)	70 (57, 86)	84 (80, 88)	77 (72, 82)	56 (48, 66)	37 (30, 47)
Subtypes								
HR+/HER2−	89 (88, 91)	80 (78, 81)	95 (92, 98)	90 (86, 94)	93 (92, 95)	87 (85, 88)	75 (72, 79)	55 (51, 59)
HER2+	86 (83, 90)	78 (74, 82)	92 (85, 99)	87 (79, 96)	92 (89, 95)	85 (81, 89)	61 (51, 73)	42 (32, 54)

Triple-negative	70 (66, 75)	62 (58, 67)	70 (60, 81)	67 (57, 79)	78 (73, 83)	71 (65, 77)	49 (39, 61)	35 (26, 47)
Not classifiable	81 (76, 86)	73 (68, 79)	88 (73, 100)	81 (64, 100)	88 (83, 94)	82 (77, 89)	59 (48, 73)	47 (36, 62)
Stage								
I	94 (93, 96)	88 (86, 90)	98 (95, 100)	97 (92, 100)	97 (96, 98)	92 (91, 94)	83 (78, 88)	66 (60, 73)
II	89 (88, 91)	80 (78, 82)	93 (90, 97)	90 (86, 94)	93 (92, 95)	87 (85, 89)	75 (71, 80)	54 (49, 59)
III	79 (76, 83)	66 (62, 70)	80 (71, 89)	70 (61, 80)	86 (83, 90)	75 (71, 80)	60 (52, 69)	37 (30, 47)
IV	25 (19, 33)	16 (11, 23)	47 (27, 80)	40 (22, 74)	31 (22, 42)	17 (11, 28)	12 (6.5, 24)	7.8 (3.4, 18)

Administrative censoring at 30 November 2023.

The HR+/HER2− subgroup exhibited OS rates of 94%/82% (stage I), 92%/72% (stage II), 84%/62% (stage III), and 29%/15% (stage IV).

For HER2+, the figures were 95%/86%, 91%/76%, 78%/60%, and 41%/28% respectively.

In TNBC, survival stood at 92%/73% (stage I), 72%/58% (stage II), 64%/41% (stage III), and 4.7% at both timepoints in stage IV.

When OS was analyzed by tumor grade—low (I-II) vs. high (III)—in HR+/HER2− cases, younger patients (<40 years) displayed significantly superior outcomes within the low-grade subset compared to middle-aged women.

Relative survival (RS) and risk factors for death

Given the lack of cause-specific death data, relative survival (RS) was computed by adjusting for age- and sex-matched population mortality.

Among patients under 70, RS at 5 and 10 years was 92% (95% CI 91-93%) and 88% (95% CI 86-89%). For those 70 or older, RS values were 82% (95% CI 78-87%) and 77% (95% CI 69-86%).

In the multivariable Cox regression, age, stage, histology, and molecular subtype independently predicted death **(Table 4)**.

Using 41-69 years as reference, the ≤40 cohort had an HR of 0.29 (95% CI 0.07-1.25, p = 0.0968), while ≥70 years had an HR of 4.90 (95% CI 3.44-6.97, p < 0.001).

The TNBC subtype showed an HR of 1.63 (95% CI 1.20-2.22, p = 0.0018**), signifying elevated mortality risk compared with HR+/HER2−.

Increasing stage and grade corresponded with higher death risk.

An interaction between age ≤40 and TNBC produced an HR of 2.25 (95% CI 1.11-4.57, p = 0.0240**), while the interaction between age ≥70 and stage IV had an HR of 0.36 (95% CI 0.20-0.63, p = 0.001).

Table 4. Multivariable Cox regression analysis identifying factors linked to mortality risk.

	Hazard Ratio	**95% CI**	***p***
	Age		
41-69	1		
≤40	0.29	0.07-1.25	0.0968
≥70	4.90	3.44-6.97	<0.001
	Subtypes		
HR+/HER2−	1		
HER2+	0.91	0.66-1.25	0.5591
Triple negative	1.63	1.20-2.22	0.0018
	Stage		
I	1		
II	1.57	1.17-2.11	0.0030
III	2.84	2.04-3.96	<0.001
IV	20.9	14.2-30.7	<0.001

Histology			
I	1		
II	1.32	1.05-1.65	0.0156
III	1.80	1.41-2.29	<0.001
Age × subtype			
≤40 × HR+/HER2−	1		
≤40 × HER2+	0.98	0.37-2.57	0.9680
≥70 × HER2+	1.17	0.73-1.87	0.5038
≤40 × Triple-negative	2.25	1.11-4.57	0.0240
≥70 × Triple-negative	0.89	0.59-1.35	0.5847
Age × Stage			
≤40 × I	1		
≤40 × II	1.26	0.28-5.61	0.7651
≥70 × II	0.95	0.63-1.44	0.8100
≤40 × III	2.85	0.64-12.7	0.1690
≥70 × III	0.69	0.43-1.10	0.1211
≤40 × IV	1.92	0.37-10.1	0.4417
≤70 × IV	0.36	0.20-0.63	<0.001

This study underscores notable age-associated disparities in breast cancer (BC) characteristics and outcomes, particularly between women aged ≤40 years and those ≥70 years. The age-specific evaluation demonstrated that younger patients tended to present with biologically aggressive tumors, reflected by a greater proportion of grade III lesions (≈45%) and a high proliferative index (Ki67 ≥20% in 69.8%). Moreover, the TNBC (19.7%) and HER2+ (16.4%) molecular profiles were disproportionately represented in this group—findings that are in line with previously reported data [6, 7].

Only 5.2% and 13.5% of patients aged ≤40 were diagnosed at stages I and II, respectively, suggesting both delayed detection and intrinsically aggressive tumor biology in this subset.

Across all molecular subtypes, 43% of younger individuals received neoadjuvant therapy, compared with 19.3% among those aged ≥70. Despite the more unfavorable tumor biology, survival outcomes remained excellent in younger patients; for stages I-III, median overall survival (OS) was not reached at either 5 or 10 years. Contrary to several reports in the literature, our findings did not indicate an inferior prognosis for younger patients [6, 16]. We speculate that equal access to care and standardized treatment protocols within our healthcare system may contribute to these encouraging outcomes. Nonetheless, young women with TNBC displayed a markedly elevated risk of death, consistent with prior evidence highlighting the aggressive course of this subtype [17, 18].

In contrast, the older cohort (≥70 years)—accounting for 22% of the total population—experienced worse survival, with 5- and 10-year OS rates of 70% (95% CI: 66-73%) and 50% (95% CI: 47-54%), respectively. Although the difference between groups was modest, it remained statistically significant, even after adjusting for non-cancer-related mortality through relative survival (RS) analysis. In our multivariable assessment, older age independently correlated with higher mortality risk, aligning with existing research that associates advanced age with poorer prognosis [19-22]. However, interpretation is complicated by the fact that elderly individuals frequently succumb to competing causes of death, often related to comorbid conditions [23, 24].

These results stress the importance of a comprehensive geriatric-oncologic approach in this demographic. Incorporating multidisciplinary evaluation and functional, comorbidity, and frailty assessments can enable treatment individualization, reduce undertreatment, and enhance both survival and quality of life [21, 25-29]. In our cohort, chemotherapy utilization was lower among the elderly, whereas Trastuzumab use remained comparable across age groups **(Table 2)**. Notably, compared with data from a Dutch population-based registry, our elderly patients showed higher chemotherapy exposure and near-universal surgical intervention for stage I-III disease, contrasting with the 66.0% surgical rate reported in that reference population [30].

Our findings further reinforce the biological diversity of breast cancer and its impact on prognosis. Patients with HR+/HER2− tumors achieved the best survival outcomes, whereas those with TNBC fared worst. The HER2+ subtype demonstrated a substantial survival improvement, likely attributable to anti-HER2-targeted therapies,

achieving a median OS comparable to HR+/HER2− cases. These data exemplify the transformative benefit of HER2-directed treatment and suggest that emerging targeted and immunotherapeutic strategies for TNBC may soon translate into measurable clinical gains as ongoing cohort studies mature.

As anticipated, tumor stage at diagnosis remained a major determinant of prognosis. The predominance of stage I-II cases in our dataset likely contributed to the overall high OS rates. However, metastatic (stage IV) disease continued to be associated with poor outcomes across all subtypes, underscoring the persistent therapeutic challenge of metastatic breast cancer and the necessity for further innovations in systemic therapy. Treatment patterns in our series mirrored current standards, with breast-conserving surgery (BCS) favored in early-stage disease and increased reliance on neoadjuvant regimens for locally advanced or biologically aggressive tumors such as TNBC and HER2+ cancers.

When comparing our data with other large-scale registries, including the American National Cancer Database (NCDB) [1] and the Japanese National Clinical Database (NCD) [3], the average age at diagnosis was found to be largely consistent across studies—58 years in our cohort versus 61 and 65 years in the NCDB and NCD, respectively.

In terms of disease stage, the proportion of stage IV cases in our population (4.8%) closely matched that of the U.S. cohort (4%), yet exceeded the Japanese figure (2.1%). Across all three datasets, early-stage disease (stages I-II) was the predominant presentation, though none provided age-stratified analyses.

When focusing on HR+/HER2− tumors, our findings revealed notable differences in overall survival (OS) between younger (<40 years) and middle-aged (41-69 years) individuals within the low-grade subgroup, with the younger patients showing superior outcomes. By contrast, Partridge *et al*. [6] reported a higher BC-specific mortality risk among young women—particularly those with low-grade HR+/HER2− cancers. This divergence highlights the need for further investigation to clarify potential biological, clinical, or healthcare-related factors influencing these variations in survival trends across cohorts.

Study Strengths and Limitations

Key strengths of our research include its extended follow-up period of over a decade, its substantial sample size, and the robustness of the clinical and epidemiological data gathered within a multicenter, single-institution framework adhering to uniform diagnostic and therapeutic standards. To our knowledge, this represents the largest breast cancer cohort ever reported in Spain.

Nevertheless, several limitations should be acknowledged. Data were unavailable for certain parameters, such as causes of death, genetic counseling outcomes, participation in clinical trials, and lifestyle-related factors, which could potentially refine the interpretation of survival outcomes.

The rapid evolution of therapeutic strategies—including CDK inhibitors, antibody-drug conjugates, immunotherapies, and next-generation anti-HER2 agents—is expected to substantially alter the prognosis of BC patients. Therefore, periodic updates to the ICO Breast Cancer Cohort would be essential to capture new treatment patterns and their long-term survival impact within a contemporary clinical context.

Conclusion

This real-world analysis offers a comprehensive overview of breast cancer epidemiology, clinicopathological profiles, treatment approaches, and long-term survival, with a specific emphasis on underrepresented age groups—patients younger than 40 and aged 70 or older.

While younger women demonstrated favorable survival outcomes (except for those with TNBC), elderly patients exhibited poorer overall survival, likely reflecting the burden of comorbid conditions.

The ICO Breast Cancer Cohort, executed within a standardized multicenter institutional setting, provides reliable and applicable evidence that can support future clinical research and foster a deeper understanding of age-related heterogeneity in breast cancer outcomes.

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