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ORIGINAL ARTICLE

Outcome of breast cancer patients with low hormone receptor positivity: analysis of a 15-year population-based cohort

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Background: Guideline recommendations for the treatment of breast cancer with low hormone receptor (HR) expression (1%-9%) are ambiguous and several studies showed more similarities with HR-negative tumors than with HR strongly positive tumors (≥10%). We used a population-based 15-year cohort to compare patient characteristics and outcome of HR low positive tumors with HR-negative and HR strongly positive tumors, respectively.

Patients and methods: A total of 38 560 women diagnosed with early invasive breast cancer between 2004 and 2018 within the scope of the Munich Cancer Registry with 4.9 million inhabitants were included. Descriptive analyses of prognostic factors, treatment, and outcome analyses using the Kaplan–Meier method; cumulative incidence in consideration of competing risks; and multivariate analyses (Cox regression and Fine–Gray model) were conducted. Endpoints were time to local recurrence (TTLR), time to lymph node recurrence (TTLNR), time to metastasis (TTM), overall survival (OS), and relative survival (RS).

Results: A total of 861 patients (2%) had HR low positive, 4862 (13%) HR-negative, and 32 837 (85%) HR strongly positive tumors. Within the HER2-negative cohort ($n = 33\ 366$), survival of HR low positive tumors was significantly worse than that of HR strongly positive tumors [OS hazard ratio 0.66 (95% confidence interval 0.55-0.78)], whereas between HR low positive and HR-negative tumors no significant survival difference could be detected [OS hazard ratio 0.93 (95% confidence interval 0.78-1.11)]. TTLR, TTLNR, and TTM showed similar results. By contrast, within the HER2-positive cohort ($n = 5194$), no statistically significant differences between the three HR groups could be detected in multivariate analyses.

Conclusion: Current definitions for HR positivity and its clinical relevance should be reconsidered. Patients with HR low positive/HER2-negative tumors could be regarded and treated similar to patients with triple-negative tumors.

Key words: breast cancer, cancer registry, hormone receptor, systemic therapy, health services research

INTRODUCTION

The hormone receptor (HR) status, including estrogen receptor (ER) and progesterone receptor (PR), is one of the most important prognostic and predictive factors in breast cancer. HR-positive tumors have a better prognosis than HR-negative tumors and they are eligible for treatment with endocrine therapy (tamoxifen and/or aromatase inhibitors).[1]

Classically, HR positivity was defined as having at least 10% nuclear staining of tumor epithelial cells. In 2010, the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) recommended ≥1% positive tumor nuclei as a threshold for HR positivity.[2] Since then, other breast cancer guidelines have adapted this new threshold, but with cautious wording concerning systemic therapy recommendations for the subgroup of low HR positivity (1%-9% positive cells). Some guidelines stated

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that for patients with HR low positive breast cancer endocrine therapy alone might be insufficient and additional neoadjuvant or adjuvant chemotherapy should be considered.[3-9]

In 2020, an update of the ASCO/CAP guideline introduced a new reporting category 'ER low positive', which is defined as 1%-10% ER positivity. Interestingly, the panel decided that this category would be determined only for ER, without including the PR status.[10]

Meanwhile, several studies showed that the prognosis of HR low positive tumors is more comparable to those with HR-negative tumors than to those with HR strongly positive tumors.[11-14] Other studies stated that to some extent HR low positive/HER2-negative tumors have similar biological and molecular characteristics as triple-negative breast cancers.[15-19]

In this study, we analyzed this topic within the context of health services research and evaluated the prognosis of the three HR subgroups in a large representative cohort comprising 15 years of primary diagnosis. We used population-based data of the Munich Cancer Registry (MCR), comprising a catchment area of 4.9 million inhabitants, to compare clinicopathological characteristics and outcome of patients with HR low positive, HR-negative, and HR strongly positive tumors, respectively.[20]

METHODS

Data collection

The MCR is the population-based clinical cancer registry of Upper Bavaria and, partly, of Lower Bavaria (Southern Germany). Its catchment area expanded from 4.3 million inhabitants in 2002 to 4.9 million since 2007.[21] Pathology reports of solid tumors from all pathology laboratories in this catchment area are available and provide the total number of breast cancer cases in the region and the respective prognostic factors. In parallel, patient demographics, prognostic factors, treatment, and follow-up information are reported from clinicians. In addition, life status of patients with a cancer diagnosis is maintained systematically through death certificates.

All data, as well as outcome measurements (e.g. death, local recurrence, metastases), are documented according to the guidelines of the International Agency for Research in Cancer. Tumors are classified according to the TNM Classification of Malignant Tumors (8th edition).[22]

Patient sample

A total of 63 947 patients with residence in the catchment area were diagnosed with a malignant breast tumor in the 15-year study period from 2004 to 2018 (Figure 1). Excluded were patients with *in situ* carcinoma, sarcoma or lymphoma, male patients, patients with primary metastasis (M1), death certificate-only cases (4%), and patients with missing data concerning HR or HER2 status. Besides, patients with evidence of another previous or synchronous malignant tumor were excluded to eliminate any overlapping tumor effects in the outcome analyses. Thus the analyses of the epidemiological cohort of 38 560 patients provide a current and population-based survey of early invasive breast cancer.

Definition of variables

During the observation period, ER and PR were assessed with immunohistochemistry (IHC) on paraffin-embedded tumor tissue.[23] To assess the HR status, the percentage of positive cells for ER and PR was used. If not available, the immunoreactive score (IRS) was used. The IRS combines staining intensity, which ranges from 0 points (no staining) to 3 points (strong staining), and the proportion of stained cells, which ranges from 0 points (no positive cells) to 4 points (>80% positive cells). The addition of the two measures results in the IRS, which results in a value between 0 and 12 points.[24] HR-negative tumors were defined as 0% positive cells for both HRs (ER and PR) or as IRS = 0. Low HR positivity was defined as between 1% and 9% positive cells for either ER or PR (or as IRS = 1) and not >9% positive cells (IRS = 0-1) for the other receptor. HR strongly positive tumors were defined as 10%-100% positive cells for ER and/or PR or as IRS = 4-12. Cases with IRS = 2-3 and missing data on the percentage of positive cells were excluded from the evaluation, as they may contain cases with >10% of positive cells with weak staining.

HER2 expression was evaluated based on IHC and *in situ* hybridization (FISH/chromogenic *in situ* hybridization) according to the ASCO/CAP guideline.[25] Cases with unclear HER2 status or missing data were excluded from the evaluation.

Accordingly, HR-negative tumors within the HER2-negative cohort equates to triple-negative tumors.

As it is not mandatory to report not conducted systemic therapies to the cancer registry, missing values had to be operationalized to the category 'no therapy'. As a result, possible therapeutic effects could be underestimated in the multivariate analyses. For the epidemiological cohort and the HER2-negative cohort, four categories for systemic therapy were generated: endocrine therapy only, chemotherapy only, endocrine therapy plus chemotherapy, and no documented therapy (including missing values). For the HER2-positive cohort, trastuzumab was additionally considered, and thus four additional categories were added to the variable: trastuzumab only, trastuzumab plus chemotherapy, trastuzumab plus endocrine therapy, and trastuzumab plus chemotherapy plus endocrine therapy. In the MCR, trastuzumab is documented since 2006. Therefore analyses containing trastuzumab could be performed for patients with diagnosis from 2006 only.

Endpoints and statistical analyses

The MCR organizes data in an Oracle database. Statistical analyses were conducted using SAS (version 9.4; SAS Institute, Cary, NC). The significance level for all analyses was set at 5%. One-way analysis of variance and the chi-square test

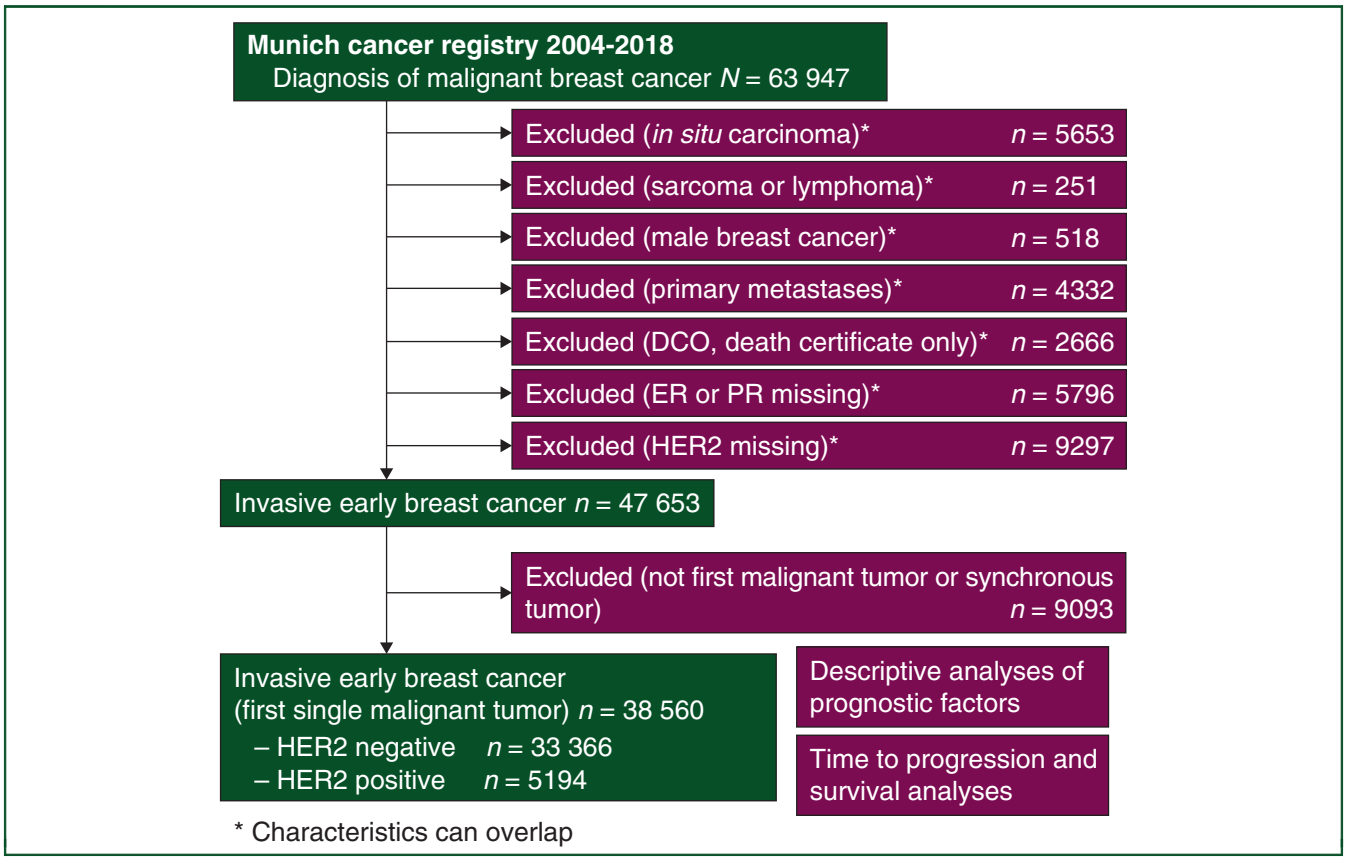


Figure 1. Study flow chart.
ER, estrogen receptor; PR, progesterone receptor.

were used to examine continuous variables and the frequency data, respectively.

Time to local recurrence (TTLR), time to lymph node recurrence (TTLNR), and time to metastasis (TTM) are surrogate parameters for survival and were therefore used as endpoints in this analysis. TTLR was chosen as an endpoint because it is a commonly used endpoint in clinical trials. TTLNR was chosen as an endpoint because there have been some changes in the surgical therapy of regional lymph nodes in recent years (comprehensive implementation of the sentinel technology, in some cases completely omitting axillary lymph node dissection) and lymph nodes are also affected by the choice of the systemic therapy. To account for death as a competing risk, cumulative incidence (CUI) analysis was used to evaluate those endpoints.[26] Univariate differences among the HR subgroups were assessed by Gray's test for equality of CUI functions, and multivariate Fine—Gray model analysis was additionally conducted.[27]

Additional endpoints in this analysis were overall survival (OS) and relative survival (RS). OS was estimated by the Kaplan—Meier method and was tested using the log-rank test. In addition, multivariate Cox proportional hazards regression was performed calculating adjusted hazard ratios. RS was computed by calculating the ratio of the observed survival rate to the expected survival rate. The expected survival time of age-matched individuals was calculated using life tables for the German population using the Ederer II method.[28] RS can be interpreted as survival from cancer after correcting for other causes of death; therefore RS was used to estimate cancer-specific survival.

To minimize selection bias survival analysis was also performed for a matched cohort for the HR-negative and the HR strongly positive group, respectively. Case matching was performed according to the distribution of age, tumor size, nodal status, and grading in the low HR group.

RESULTS

Tumor characteristics and treatment

The population-based cohort comprised 38 560 female patients with a diagnosis of early invasive breast cancer between 2004 and 2018; 861 patients (2%) had HR low positive, 4862 (13%) HR-negative, and 32 837 (85%) strongly HR-positive tumors. Selected patient and tumor characteristics stratified by HR status are presented in Table 1. Whereas the distribution of tumor characteristics was quite similar between the HR low positive and the HR-negative subgroup, considerable differences between the HR low positive and HR strongly positive subgroup could be shown. Patients with HR strongly positive tumors were older, had smaller tumors, more grade 1 tumors, less HER2-positive tumors, and a higher proportion of invasive lobular histology. The use of systemic therapy was different in the three HR groups. The proportion of endocrine therapy was 87% in the HR strongly positive group, 45% in the low HR-positive group, and 5% in the HR-negative group. Regarding

Table 1. Tumor characteristics for women with early invasive breast cancer according to hormone receptor (HR) status ($N = 38\ 560$)

Characteristics	HR negative ($n = 4862$; 13%), n (%)[a]	HR low positive ($n = 861$; 2%), n (%)[a]	HR strongly positive ($n = 32\ 837$; 85%), n (%)[a]	P value χ^2 low versus negative	P value χ^2 low versus strongly
Age (years)				0.2689	<0.0001
Mean (SD)	58 (15)	57 (15)	62 (14)		
<50	1552 (32)	277 (21)	6907 (21)		
50-59	1150 (24)	216 (25)	7484 (23)		
60-69	1019 (21)	194 (23)	8919 (27)		
70-79	760 (16)	112 (13)	6263 (19)		
≥80	381 (8)	62 (7)	3264 (10)		
c/p T category[b]				0.2937	<0.0001
T1	1815 (39)	331 (40)	18 578 (58)		
T2	2162 (46)	387 (46)	10 805 (34)		
T3	374 (8)	52 (6)	1435 (5)		
T4	335 (7)	67 (8)	1244 (4)		
n.a.	176 (4)	24 (3)	775 (2)		
c/p N category[b]				0.9668	0.2637
N0	3211 (69)	571 (69)	20 877 (67)		
N+	1474 (32)	263 (32)	10 462 (33)		
NX/n.a.	177 (4)	27 (3)	1498 (5)		
Grading				0.0098	<0.0001
G1	46 (1)	10 (1)	5203 (16)		
G2	1313 (27)	273 (32)	21 429 (66)		
G3	3448 (72)	564 (67)	6027 (19)		
GX/n.a.	55 (1)	14 (2)	178 (1)		
HER2/neu status				0.0039	<0.0001
HER2/neu negative	3364 (69)	553 (64)	29 449 (90)		
HER2/neu positive	1498 (31)	308 (36)	3388 (10)		
Histology				0.0006	<0.0001
Invasive ductal	4343 (89)	753 (88)	26 239 (78)		
Invasive lobular	87 (2)	33 (4)	4887 (15)		
Other	428 (9)	74 (9)	1676 (5)		
n.a.	4 (0)	1 (0)	35 (0)		
Systemic therapy				<0.0001	<0.0001
None	967 (20)	117 (14)	3256 (10)		
ET only	50 (1)	79 (9)	18 422 (56)		
CT only	3637 (75)	356 (41)	1136 (4)		
ET + CT	208 (4)	309 (36)	10 023 (31)		

CT, chemotherapy; ET, endocrine therapy; n.a., not available; SD, standard deviation.
[a] Column percentage can differ slightly from 100% due to rounding.
[b] For patients with neoadjuvant therapy, cTNM was used.

the treatment with chemotherapy, proportions were 34%, 77%, and 79%, respectively.

In the subgroup of HER2-negative tumors, the results were comparable (Table 2). However, in the HER2-positive cohort, the differences were less pronounced (see Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.08.1988).

Survival analysis

Median follow-up time was 71 months (range 0-185 months). To consider differences in treatment indication, survival analysis was conducted separately for HER2-positive and HER2-negative tumors. First, surrogate parameters for survival such as TTLR, TTLNR, and TTM have been analyzed. Figure 2 shows the curves for the CUI of TTLR, separately for the HER2-negative and the HER2-positive cohort. In the HER2-negative subgroup, the curves of HR low positive and HR-negative tumors were almost identical, but the CUI of TTLR in the HR strongly positive group was significantly lower (10-year CUI: HR negative 14.0%, HR low positive 13.2%, HR strongly positive 6.9%). In the subgroup of HER2-positive tumors, the difference between the HR low positive and the HR strongly positive group was observably smaller, and not statistically significant. The 10-year CUI was 10.8%, 10.5%, and 9.5%, respectively.

The same scheme was observable in TTLNR and TTM: identical curves of HR low positive and HR-negative tumors, and significantly different curves of HR strongly positive tumors in the HER2-negative subgroup; in the HER2-positive subgroup only slight differences could be shown, but in a similar pattern (Figures 3 and 4). The multivariate analyses (Fine—Gray models) confirmed the univariate results, respectively (for the HER2-negative subgroup, see Table 3; for the HER2-positive subgroup, see Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.08.1988).

According to the results of the surrogate parameters, curves for OS and RS also showed the same pattern (Figure 5). In the HER2-negative subgroup, the 10-year OS was 66% for HR-negative cases, 65% for HR low positive cases, and 75% for HR strongly positive. In the HER2-positive subgroup, these were 72%, 73%, and 74%, respectively. The multivariate Cox regression analysis also confirmed these results. In the HER2-negative cohort, the adjusted hazard ratio for HR-negative tumors was 0.93 [95%

Table 2. Tumor characteristics for women with early invasive breast cancer according to hormone receptor (HR) status (HER2 negative, $N = 33\ 366$)

Characteristics	HR negative ($n = 3364$; 10%), n (%)[a]	HR low positive ($n = 553$; 2%), n (%)[a]	HR strongly positive ($n = 29\ 449$; 88%), n (%)[a]	P value χ^2 low versus negative	P value χ^2 low versus strong
Age (years)				0.3663	<0.0001
Mean (SD)	58 (15)	57 (15)	63 (13)		
<50	1112 (33)	197 (36)	5843 (20)		
50-59	738 (22)	130 (24)	6684 (23)		
60-69	701 (21)	111 (20)	8146 (28)		
70-79	532 (16)	79 (14)	5792 (20)		
≥80	281 (8)	36 (7)	2984 (10)		
c/p T category[b]				0.1785	<0.0001
T1	1258 (39)	204 (38)	17 057 (59)		
T2	1533 (47)	271 (51)	9441 (33)		
T3	256 (8)	29 (5)	1240 (4)		
T4	201 (6)	32 (6)	1061 (4)		
n.a.	116 (4)	17 (3)	650 (2)		
c/p N category[b]				0.9330	0.0806
N0	2288 (71)	379 (71)	18 856 (67)		
N+	956 (30)	157 (29)	9232 (33)		
NX/n.a.	120 (4)	17 (3)	1361 (5)		
Grading				0.0312	<0.0001
G1	33 (1)	10 (2)	5086 (17)		
G2	797 (24)	151 (28)	19 643 (67)		
G3	2505 (75)	386 (71)	4569 (16)		
GX/n.a.	29 (1)	6 (1)	151 (1)		
Histology				0.0018	<0.0001
Invasive ductal	2927 (87)	465 (84)	23 152 (79)		
Invasive lobular	69 (2)	25 (5)	4706 (16)		
Other	366 (11)	63 (11)	1557 (5)		
n.a.	2 (0)	0 (0)	34 (0)		
Systemic therapy				<0.0001	<0.0001
None	687 (20)	71 (13)	3006 (10)		
ET only	37 (1)	61 (11)	17 645 (60)		
CT only	2521 (75)	224 (41)	848 (3)		
ET + CT	119 (4)	197 (36)	7950 (27)		

CT, chemotherapy; ET, endocrine therapy; n.a., not available; SD, standard deviation.
[a] Column percentage can differ slightly from 100% due to rounding.
[b] For patients with neoadjuvant therapy, cTNM was used.

confidence interval (CI) 0.78-1.11], and for HR strongly positive tumors, it was 0.66 (95% CI 0.55-0.78; Table 3). In the HER2-positive subgroup, the values were 0.81 (95% CI 0.59-1.08) and 0.80 (95% CI 0.59-1.08), respectively (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.08.1988).

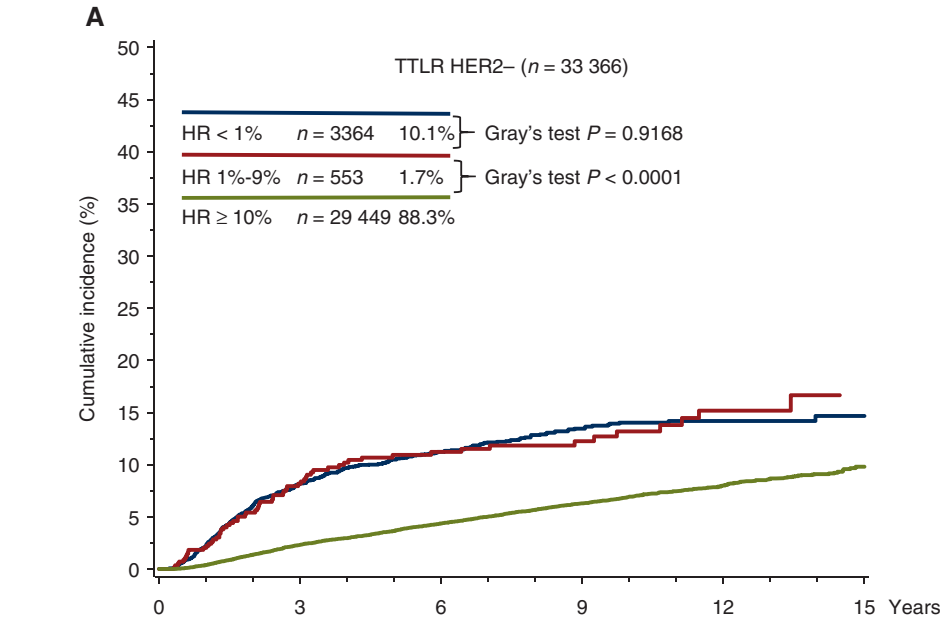
In a matched cohort analysis of HR-negative tumors and HR strongly positive tumors, no significant survival difference could be shown between low HR-positive tumors and HR-negative tumors (log-rank test, $P = 0.7543$). On the contrary, survival in the HR strongly positive cohort was significantly better than in the low HR-positive cohort (log-rank test, $P < 0.0001$) (data not shown).

A total of 47% of the HER2-negative/HR low positive patients and 42% of the HER2-positive/HR low positive patients were treated with endocrine therapy. To estimate the effect of endocrine therapy on patients with low HR-positive tumors, an additional survival analysis was performed. In the HER2-negative/low HR-positive cohort, the Kaplan—Meier curves showed a slight benefit from endocrine therapy, but this effect was not statistically significant with an adjusted hazard ratio of 0.78 (95% CI 0.55-1.11). However, in the HER2-negative/strongly positive cohort this survival difference was greater and statistically significant with a resulting adjusted hazard ratio of 0.73 (95% CI 0.68-0.78). This pattern could be also shown in the HER2-positive cohort (Figure 6). Overall, irrespective of HER2 status patients with low HR-positive tumors seem not to benefit from endocrine therapy.

DISCUSSION

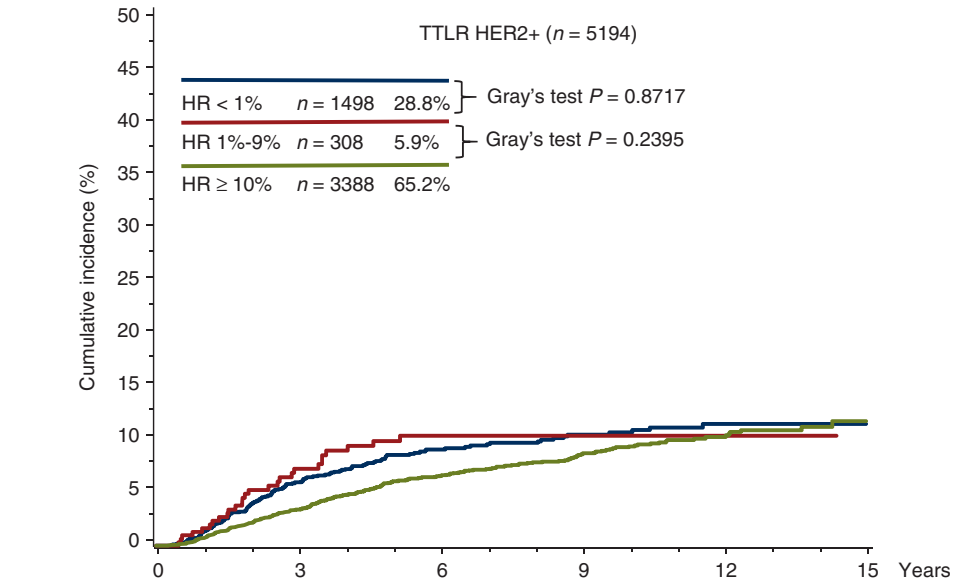
In this study, we used a 15-year population-based cohort to evaluate clinicopathological factors and outcome of HR low positive tumors compared with HR-negative and HR strongly positive tumors, respectively. The distribution of tumor characteristics between the HR groups were similar for HER2-negative and HER2-positive tumors, respectively. For outcome parameters, however, clear differences were apparent. In the HER2-negative cohort prognosis of HR low positive tumors was similar to that of HR-negative tumors, whereas in the HER-positive cohort the differences were less pronounced. One explanation could be that the effect of the anti-HER2 therapy is so strong that prognostic factors such as HR expression have a lowered impact on outcome.

This analysis comprises 861 HR low positive breast cancer cases with a median follow-up of 71 months and is one of the largest cohorts analyzed so far. In addition, data from a population-based cancer registry was used, therefore the



Patients at risk (censored)

HR < 1%	3364 (0)	2068 (611)	1274 (1177)	707 (646)	273 (2051)	27 (2289)
HR 1%-9%	553 (0)	361 (92)	244 (168)	144 (248)	64 (316)	
HR ≥ 10%	29 449 (0)	21 614 (5697)	14 364 (11 108)	8162 (16 047)	3183 (20 371)	317 (23 036)



Patients at risk (censored)

HR < 1%	1498 (0)	1043 (245)	652 (520)	385 (746)	157 (950)	11 (1090)
HR 1%-9%	308 (0)	192 (60)	128 (104)	85 (142)	41 (180)	
HR ≥ 10%	3388 (0)	2455 (621)	1629 (1197)	952 (1741)	407 (2207)	43 (2252)

Figure 2. Cumulative incidence of time to local recurrence (TTLR) for patients with HER2-negative (A) and HER2-positive tumors (B), stratified by hormone receptor (HR) status.

patient collective represents real-life data and renders the results highly representative for clinical practice.

Mean age was comparable to studies using similar inclusion criteria.[11,18,19] However, in studies using only patients with neoadjuvant chemotherapy mean age was younger.[12,14,29,30]

The outcome results of this study follow prior evidence reported elsewhere. Fujii et al.[31] presented OS curves for

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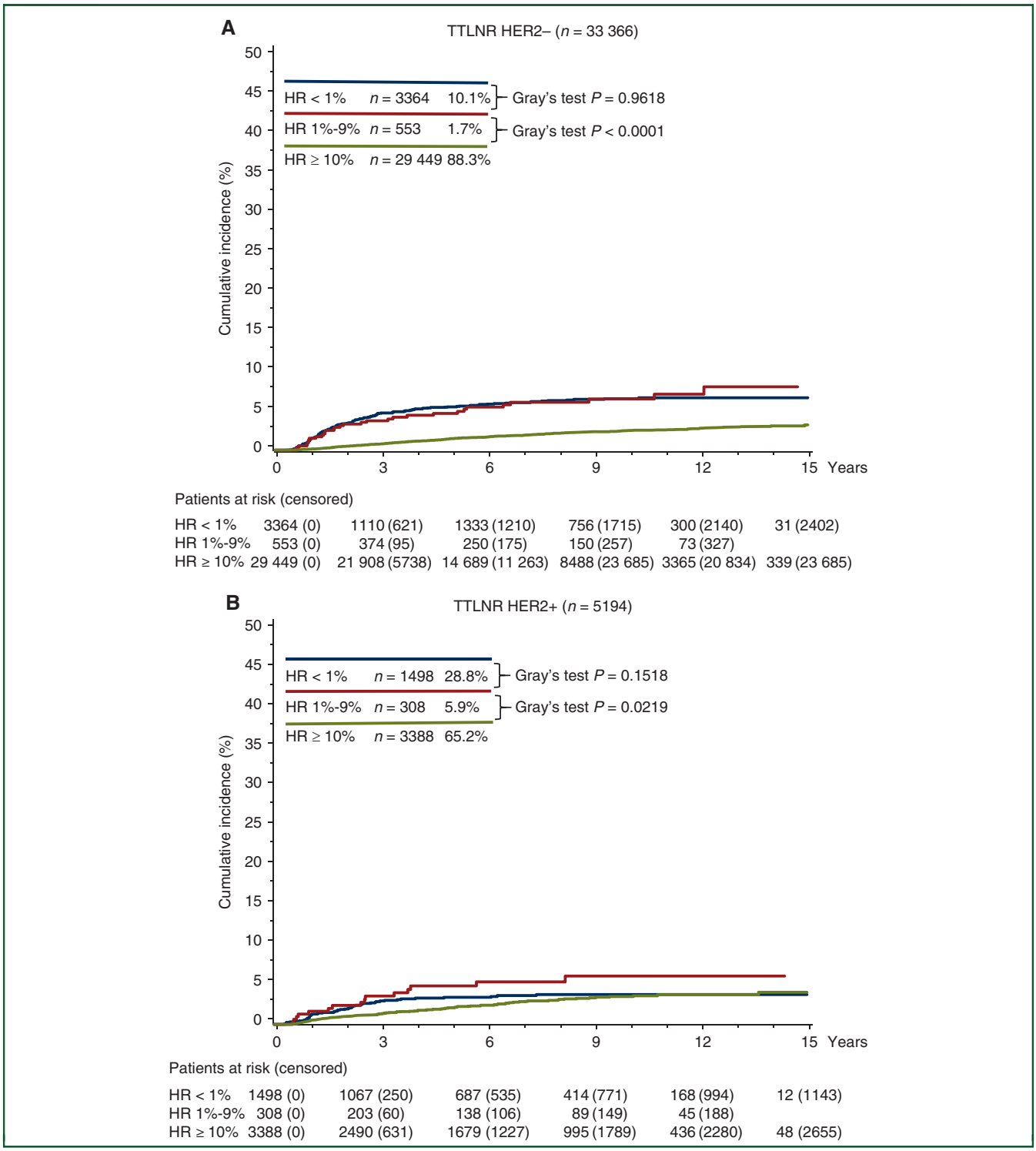

Figure 3. Cumulative incidence of time to lymph node recurrence (TTLNR) for patients with HER2-negative (A) and HER2-positive tumors (B), stratified by hormone receptor (HR) status.

171 patients with HR low positive/HER2-negative tumors who received neoadjuvant chemotherapy. Because of different inclusion criteria, the survival probabilities were lower than those in the MCR data set [5-year OS 62% (Fujii) versus 74% (MCR)] but followed the same pattern. Similar outcome results were also shown by other authors.[12,13] Furthermore, results from studies evaluating different endpoints confirm the similarity of HR low positive tumors with HR-negative tumors. Several studies compared pathologic complete response between the three HR groups and found that the pathologic complete response was significantly higher in HR low positive tumors than in HR strongly positive tumors.[14,18,31,32] Deyarmin et al.,[15] Iwamoto et al.,[16] and Villegas et al.[32] generated gene expression data for ER low positive tumors and found that most of them were basal-like which is more typical for ER-negative

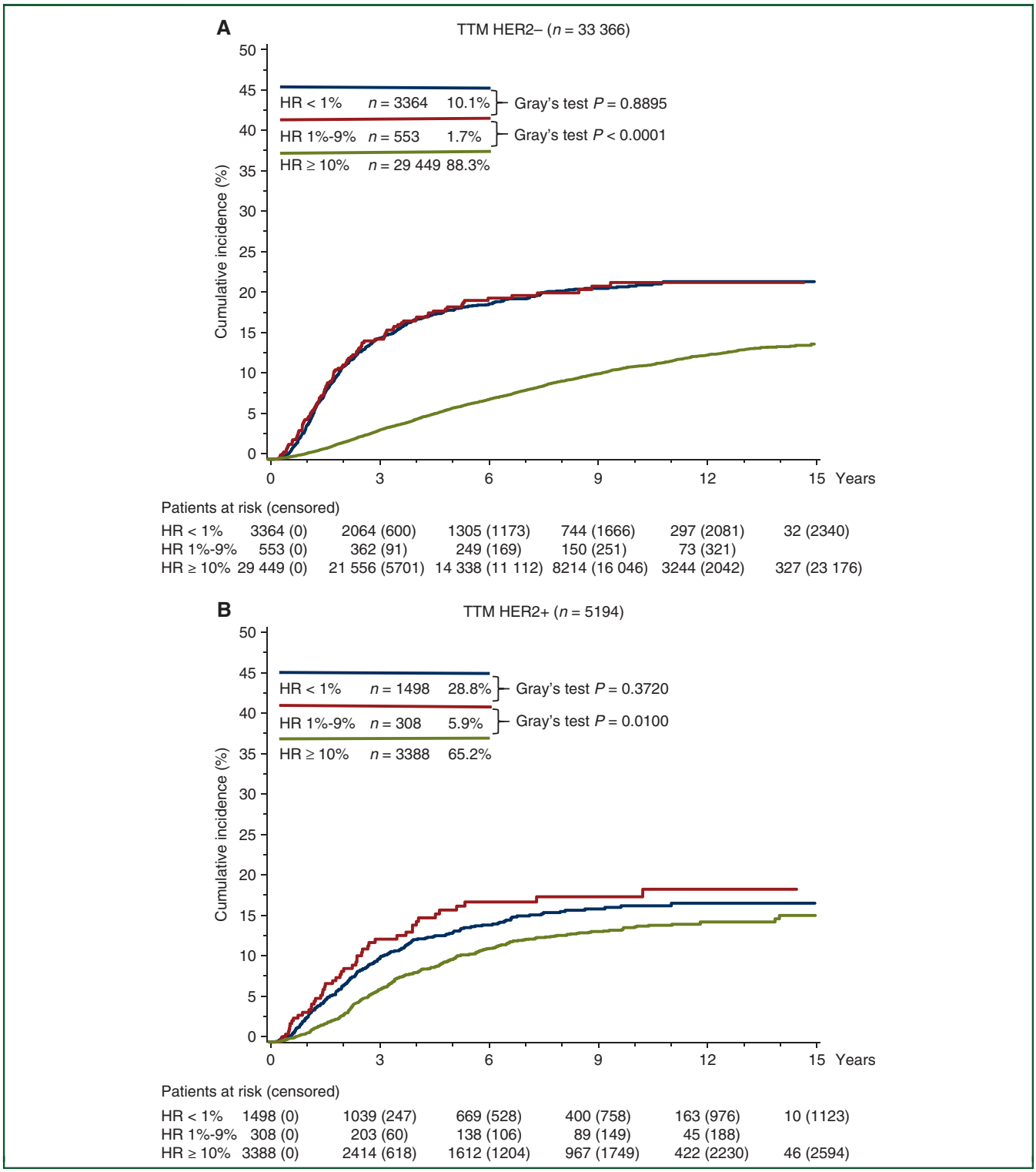

Figure 4. Cumulative incidence of time to distant metastases (TTM) for patients with HER2-negative (A) and HER2-positive tumors (B), stratified by hormone receptor (HR) status.

tumors. Sanford et al.[17] found a similar incidence of g*BRCA* 1/2 mutation between HR low positive and HR-negative tumors. Because of the nature of retrospective data, the observed survival difference between low HR-positive tumors and HR strongly positive tumors could theoretically be due to random differences in the distribution of prognostic factors. A matched cohort analysis based on the distribution of age, stage, and grading in the low HR positive cohort lead to similar results as the multivariate Cox regression analysis. Therefore one could assume that there is a biological similarity between low HR-positive tumors and HR-negative tumors.

Endocrine therapy was offered to 87% of patients with HR strongly positive tumors, but only to 45% of patients with low HR-positive tumors. One possible reason could be unclear guideline recommendations for low HR-positive

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Table 3. Multivariate Cox regression model for overall survival (OS) and multivariate Fine–Gray models for time to local recurrence (TTLR), time to lymph node recurrence (TTLNR), and time to metastasis (TTM) for patients with invasive early breast cancer (HER2 negative, $N = 33\ 366$)

	Cox regression OS (Events: 6188), adjusted HR (95% CI)	Fine–Gray model TTLR (Events: 1914), adjusted HR (95% CI)	Fine–Gray model TTLNR (Events: 750), adjusted HR (95% CI)	Fine–Gray model TTM (Events: 3085), adjusted HR (95% CI)
Hormone receptor status	$P < 0.0001$*	$P = 0.0003$*	$P = 0.0005$*	$P < 0.0001$*
Negative	0.93 (0.78-1.11)	0.88 (0.66-1.16)	0.86 (0.58-1.28)	0.95 (0.76-1.20)
Low positive	Ref.	Ref.	Ref.	Ref.
Strongly positive	0.66 (0.55-0.78)	0.62 (0.47-0.83)	0.53 (0.35-0.80)	0.59 (0.47-0.75)
Age (years)	$P < 0.0001$*	$P < 0.0001$*	$P < 0.0001$*	$P < 0.0001$*
<50	Ref.	Ref.	Ref.	Ref.
50-59	1.14 (1.02-1.26)	0.60 (0.52-0.68)	0.77 (0.63-0.95)	0.92 (0.84-1.02)
60-69	1.59 (1.44-1.74)	0.50 (0.44-0.57)	0.62 (0.51-0.77)	0.82 (0.74-0.91)
70-79	2.95 (2.68-3.25)	0.47 (0.44-0.55)	0.46 (0.36-0.59)	0.75 (0.67-0.85)
≥80	7.22 (6.50-8.02)	0.36 (0.29-0.44)	0.25 (0.17-0.35)	0.37 (0.30-0.45)
pT/cT category[a]	$P < 0.0001$*	$P < 0.0001$*	$P < 0.0001$*	$P < 0.0001$*
T1	Ref.	Ref.	Ref.	Ref.
T2	1.78 (1.67-1.90)	1.45 (1.30-1.61)	1.95 (1.62-2.33)	2.09 (1.91-2.28)
T3	2.62 (2.36-2.90)	1.46 (1.18-1.80)	1.85 (1.33-2.56)	2.99 (2.60-3.44)
T4	3.35 (3.05-3.68)	1.59 (1.27-2.00)	1.84 (1.31-2.57)	3.57 (3.07-4.15)
n.a.	3.41 (3.01-3.87)	1.09 (0.79-1.49)	1.41 (0.88-2.27)	2.65 (2.14-3.28)
pN/cN category[a]	$P < 0.0001$*	$P < 0.0001$*	$P < 0.0001$*	$P < 0.0001$*
N0	Ref.	Ref.	Ref.	Ref.
N+	1.85 (1.74-1.96)	1.44 (1.29-1.61)	1.99 (1.67-2.36)	2.65 (2.43-2.89)
NX/n.a.	2.23 (2.04-2.45)	1.59 (1.24-2.04)	2.19 (1.49-3.22)	1.37 (1.09-1.73)
Grading	$P < 0.0001$*	$P < 0.0001$*	$P < 0.0001$*	$P < 0.0001$*
G1	Ref.	Ref.	Ref.	Ref.
G2	1.32 (1.20-1.45)	1.60 (1.35-2.55)	2.14 (1.52-3.02)	2.64 (2.15-3.23)
G3	1.76 (1.58-1.96)	2.09 (1.71-2.55)	3.62 (2.48-5.28)	3.82 (3.08-4.74)
GX/n.a.	1.58 (1.22-2.03)	2.98 (1.94-4.58)	5.57 (2.87-10.84)	5.52 (3.69-8.26)
Histology	$P = 0.0007$*	$P = 0.0779$*	$P < 0.0001$*	$P < 0.0001$*
Invasive ductal	Ref.	Ref.	Ref.	Ref.
Invasive lobular	0.98 (0.91-1.06)	0.84 (0.73-0.98)	0.55 (0.41-0.72)	0.95 (0.85-1.06)
Other	0.80 (0.72-0.89)	0.88 (0.72-1.07)	0.67 (0.47-0.94)	0.62 (0.51-0.75)
n.a.	0.76 (0.43-1.35)	0.71 (0.17-3.08)	0.00 (0.00-0.00)	1.36 (0.56-3.31)
Systemic therapy	$P < 0.0001$*	$P < 0.0001$*	$P < 0.0001$*	$P = 0.0002$*
CT only	Ref.	Ref.	Ref.	Ref.
ET only	0.92 (0.83-1.03)	1.07 (0.87-1.31)	1.23 (0.91-1.67)	0.85 (0.73-1.00)
CT and ET	0.72 (0.64-0.81)	0.75 (0.61-0.91)	0.72 (0.54-0.96)	0.99 (0.86-1.14)
None	1.26 (1.13-1.40)	2.06 (1.70-2.50)	2.03 (1.56-2.65)	1.15 (0.98-1.35)

CI, confidence interval; CT, chemotherapy; ET, endocrine therapy; HR, hazard ratio; n.a., not available; Ref., reference.
*Wald test.
[a] For patients with neoadjuvant therapy, cTNM was used.

tumors. Another reason could be the growing evidence for the thesis of biological similarity of low HR-positive tumors to HR-negative tumors during the observation period.[13,17-19] To evaluate the benefit of endocrine therapy for patients with HR low positive tumors, we compared survival of low HR tumors with and without endocrine therapy. The results show that patients with low HR-positive tumors seem to benefit only slightly from endocrine therapy, but this difference was not statistically different. There are only a few studies which addressed the effect of endocrine therapy. In the analysis of the Early Breast Cancer Trialists' Collaborative Group, no statistically significant benefit of tamoxifen on the recurrence rate could be shown for ER-poor tumors.[33] Bouchard-Fortier et al.[11] analyzed the effect of endocrine therapy in several groups of ER levels and found that up to <10 fmol/mg there was no significant effect on breast cancer-specific survival. In the analysis of Ding et al.[12] patients without endocrine therapy had poorer disease-free and OS than patients with endocrine therapy, although this difference was not statistically significant. Overall, patients with low HR-positive tumors seem not to benefit significantly from endocrine therapy, irrespective of HER2 status.

The current 2020 ASCO/CAP guideline defined a new 'ER low' category as a first step for stratified therapy decisions.[10] It should be noted that this category is not completely identical with our 'HR low' category, which also included the PR status.

To exclude a potential threshold effect, we also conducted an analysis with a categorical variable splitting the low HR group at 5% staining cells into four subgroups (data not shown). The distribution of prognostic factors, outcome, and the benefit of endocrine therapy were similar in the HR-negative, 1% to <5%, and 5% to <10% groups. Therefore a potential threshold effect was not apparent to differentiate endocrine-responsive tumors from non-endocrine-responsive tumors. In theory, the use of more sensitive methods for IHC staining could lead to stage migration bias. However, in the pathology departments reporting to the MCR the implemented IHC methods did not change substantially during the observation period. Quality control also included regular plausibility checks and the use of positive

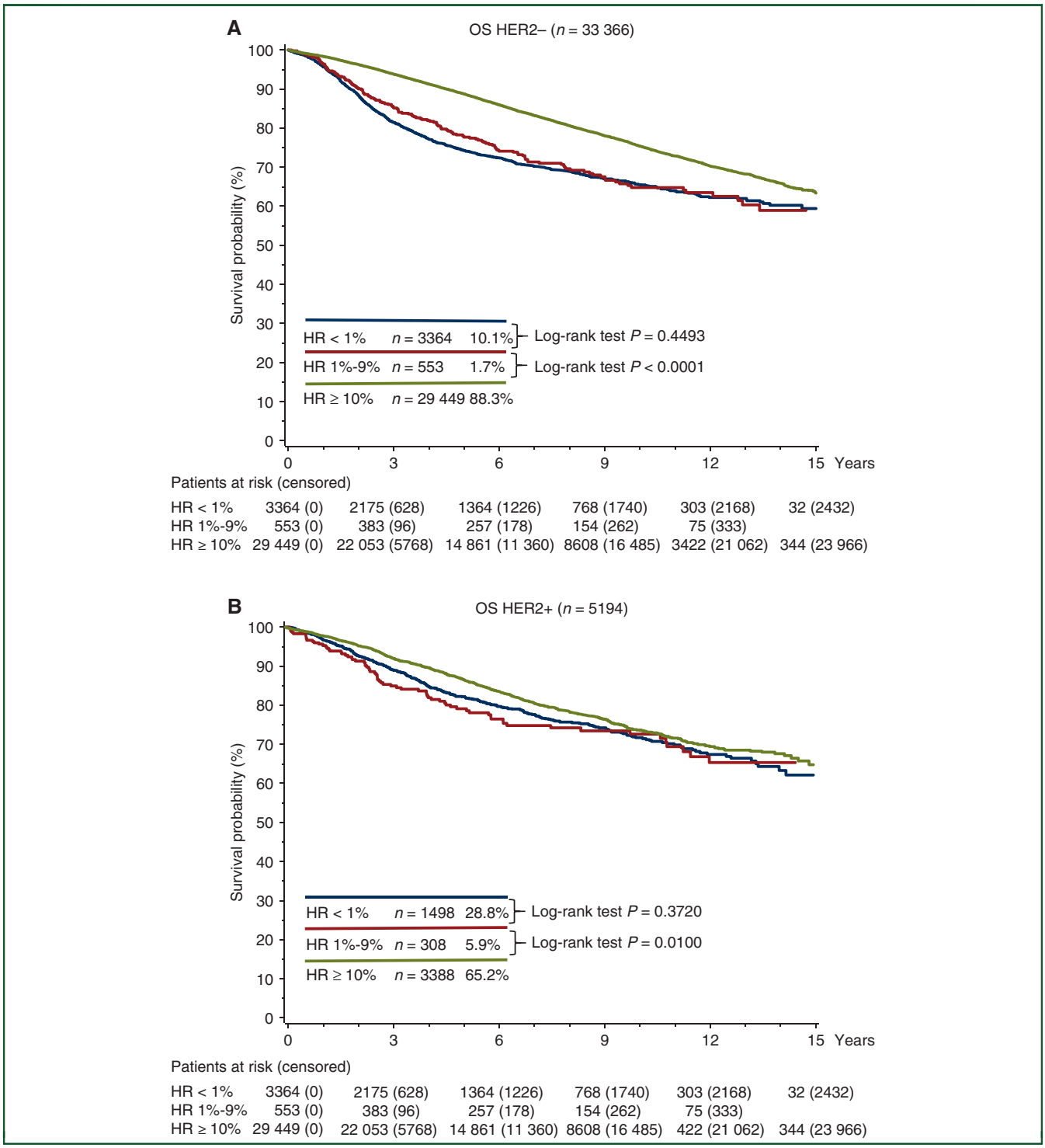

Figure 5. **Overall survival (OS) for patients with HER2-negative (A) and HER2-positive tumors (B), and relative survival (RS) for patients with HER2-negative (C) and HER2-positive tumors (D), stratified by hormone receptor (HR) status.**

controls. Because of the semiquantitative nature of the assessment of hormone receptors assessment results close to thresholds, for example, 1% or 9% stained cells for ER are rechecked by a separate senior physician. Thus the probability of false-positive results in the low HR positive group can be reduced to a minimum. In addition, most pathology departments take part in German proficiency testing programs such as the Quality Assurance Initiative for Pathology.[34] Looking at the data the proportions for each of the HR-categories did not change significantly between 2004 and 2018. Therefore no evidence suggests that the observed similarity between low HR-positive tumors and HR-negative tumors is affected by changes in IHC testing or differences between pathology departments.

Despite several strengths of the presented evaluation (a large number of HR low positive tumors, population-based

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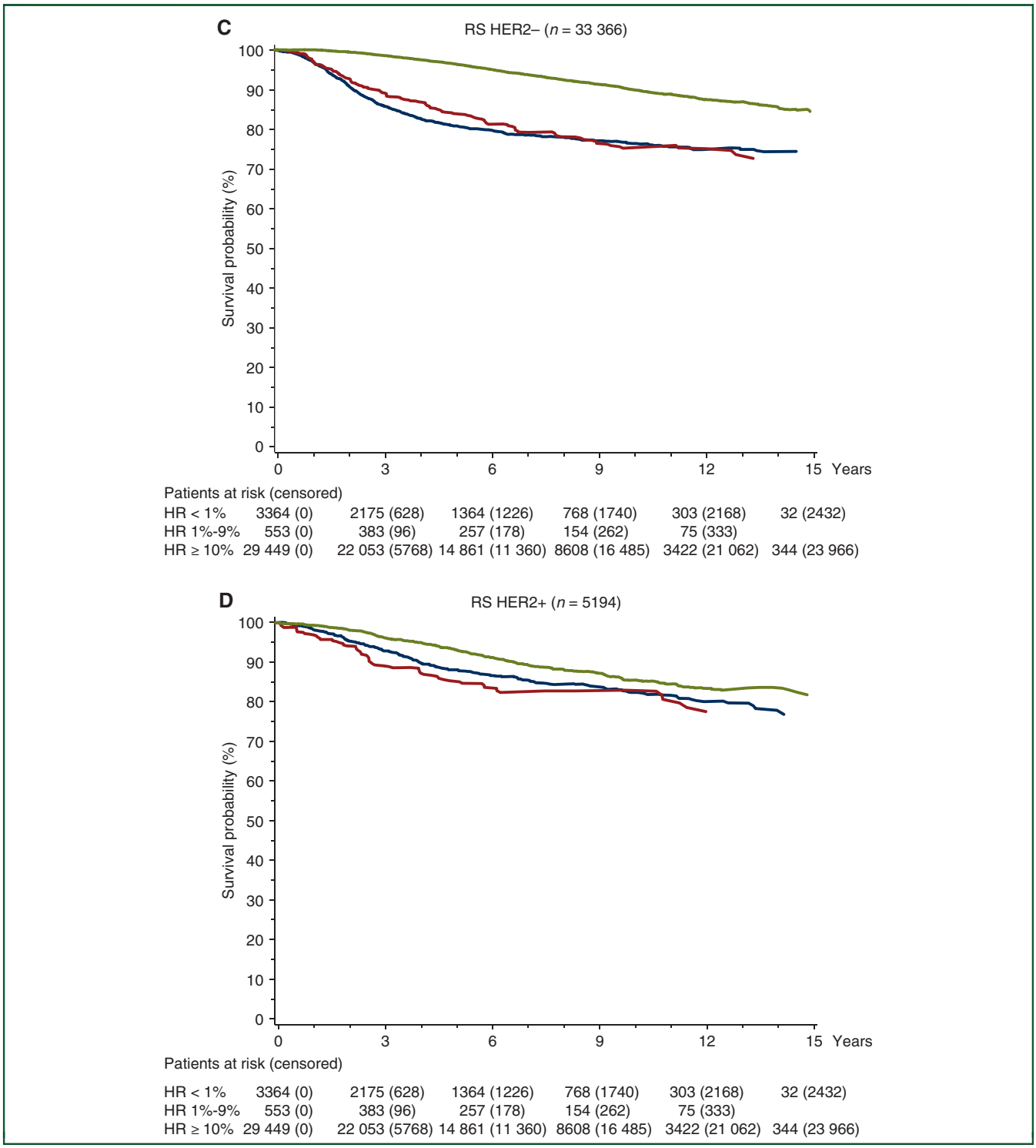

Figure 5. Continued.

analysis, large catchment area, long follow-up), relevant limitations need to be mentioned. This is a cohort study and could therefore be biased by known or unknown confounders. Comorbidity or socioeconomic status could be relevant factors influencing the survival of breast cancer patients. These factors are not reported to the cancer registry and could therefore not be included in the multivariate analyses.

Another limitation is the possible underestimation of systemic therapy effects as a result of the inherent underreporting of therapies (particularly therapies not conducted, as well as those conducted but not reported) in the cancer registry, as mentioned in the 'Methods' section. However, with the stepwise implementation of certified breast centers in Germany, since 2006 data quality has increasingly improved, and therefore this bias may be only

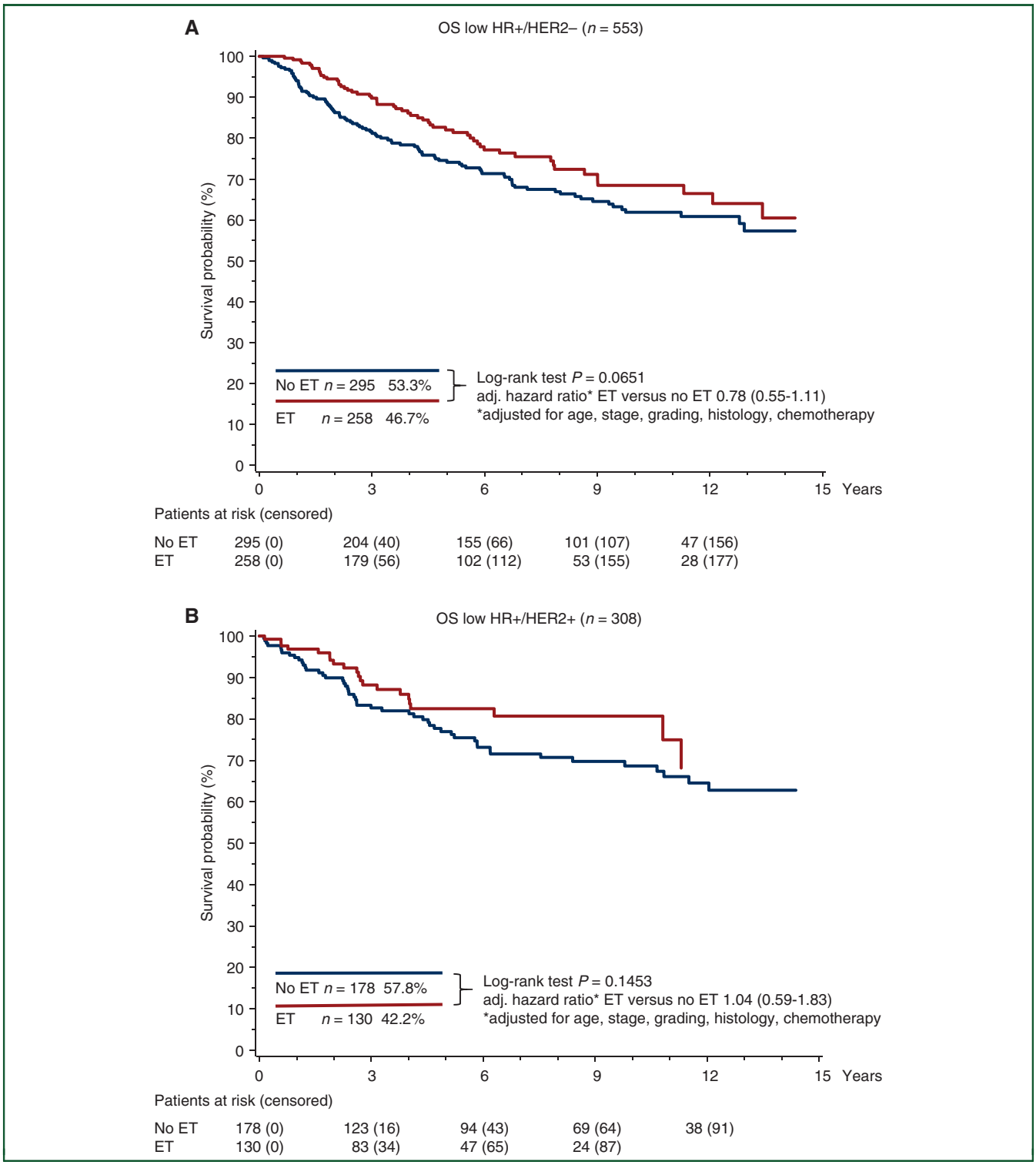

Figure 6. **Overall survival (OS) for patients with low hormone receptor (HR)-positive/HER2-negative (A) and low HR-positive/HER2-positive tumors (B), and relative survival (RS) for patients with low HR-positive/HER2-negative (C) and low HR-positive/HER2-positive tumors (D), stratified by endocrine therapy (ET).**

marginally relevant. Finally, a few implausible values are apparent in the systemic therapy variable such as a documented endocrine therapy in the HR-negative cohort, but this is not unusual in real-life data documented to the cancer registry.

Conclusion

The results of our study based on data of a large, representative 15-year cohort of 38 560 breast cancer patients showed similar prognosis of HR low positive and HR-negative tumors, particularly in the HER2-negative

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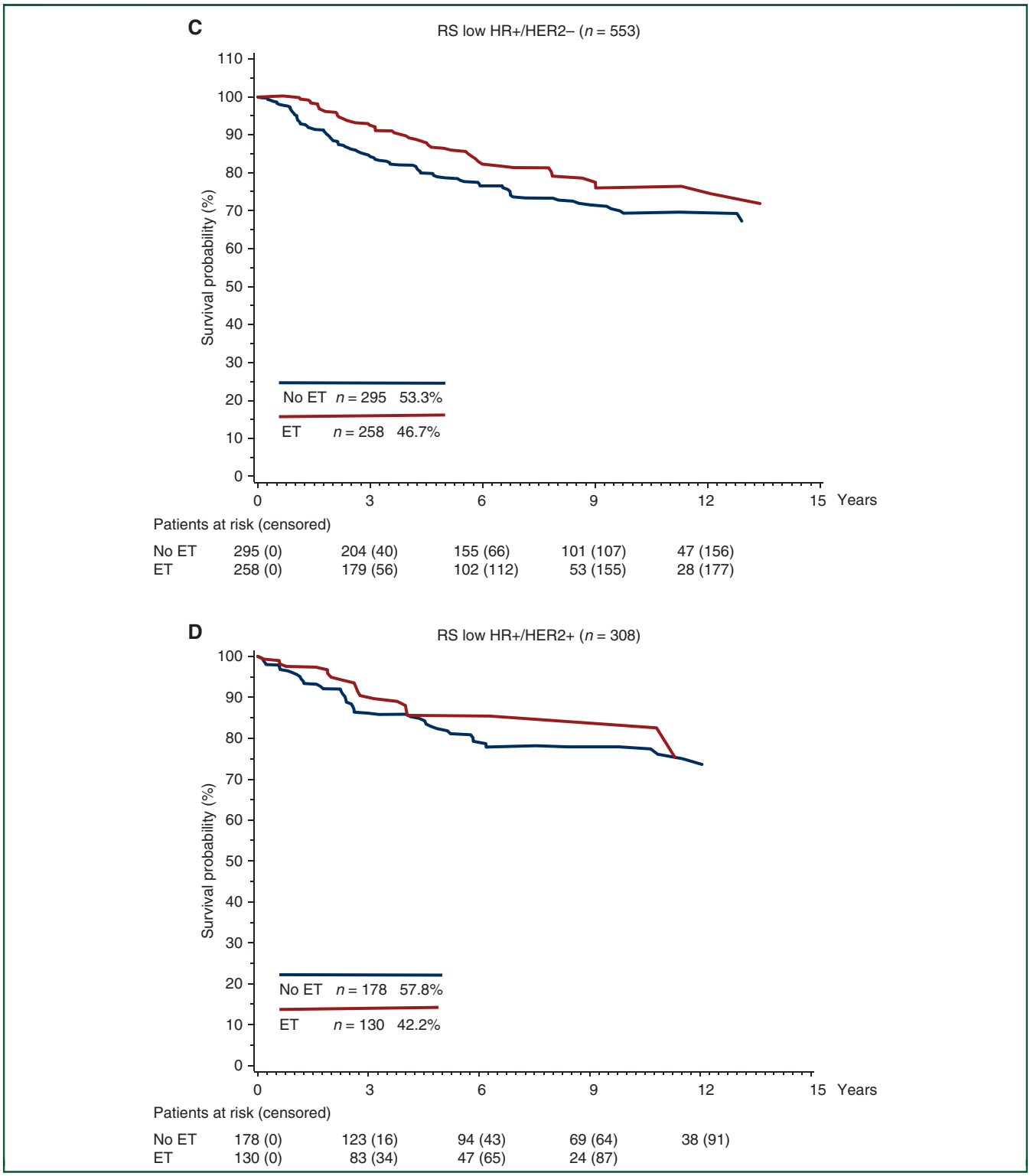

Figure 6. **Continued.**

cohort. Therefore current definitions for HR positivity and its clinical relevance should be reconsidered. Patients with HR low positive/HER2-negative tumors could be regarded and treated similar to patients with triple-negative tumors. Potentially, a prospective RCT will need to replicate these findings to determine an improved treatment stratification scheme for these patient groups.

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DISCLOSURE

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ETHICAL APPROVAL

For the evaluation, anonymized patient data was used, therefore this retrospective study does not require ethics approval.

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