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Association of triple positivity with prognostic parameters and overall survival in a population-based study of 6,122 HER2-positive breast cancer patients: analysis of real-world clinical practice based on a research database

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Triple-positive breast cancer (TPBC), i.e. HER2-positive (HER2+) and hormone receptors-positive breast cancer, is a specific subgroup of breast cancers. TPBC biology is characterized by strong mutual interactions between signaling pathways stimulated by estrogens and HER2 amplification. The present study aims to carry out a population-based analysis of treatment outcomes in a cohort of hormone receptor (HR) positive and negative breast cancer patients who were treated with anti-HER2 therapy in the Czech Republic. The BREAST research database was used as the data source for this retrospective analysis. The database covers approximately 95% of breast cancer patients treated with targeted therapies in the Czech Republic. The analysis included 6,122 HER2-positive patients. The patients were divided into two groups, based on estrogen receptor (ER) or progesterone receptor (PR) positivity: hormone receptor negative (HR-) patients had both ER- and PR-negative tumors (n=2,518), unlike positive (HR+) patients (n=3,604). HR+ patients were more often diagnosed premenopausal at the time of diagnosis, presented more often at stage I or II and their tumors were less commonly poorly differentiated. The overall survival (OS) was significantly higher in subgroups of HR+ patients according to treatment setting. When evaluated by stages, significantly higher OS was observed in HR+ patients diagnosed at stages II, III, and IV and regardless of tumor grade.

Key words: breast cancer, triple positive, HER2-positive, hormone receptors, trastuzumab, overall survival

Advances in the diagnosis and adjuvant therapy have resulted in a decrease in breast cancer mortality [1–3]. Personalized therapy relies on the evaluation of clinical and pathological parameters predicting the prognosis, response to therapy and toxicity, including the patient's age, presence of comorbidities, clinical stage as well as tumor biomarkers such as the expression of hormone receptors (HR) or the human epidermal growth factor receptor 2 (HER2). These parameters routinely determine the management of newly diagnosed breast cancer cases [4].

In general, the expression of estrogen receptors (ER) and progesterone receptors (PR) is associated with better outcomes. Overall survival (OS), disease-free survival, or time to progression are positively affected by the expression of ER and PR [5–7]. However, it should be noted that although the initial relapse rate is higher in ER-negative (ER–) tumors during the first five years after diagnosis, results of long-term follow-up have shown a higher frequency of late relapses in ER-positive (ER+) tumors [8, 9]. HER2 amplification is a biomarker of poor prognosis in patients not treated with anti-HER2 therapy [10–12].

Triple-positive breast cancer (TPBC), i.e. HER2-positive (HER2+) and HR-positive (HR+) breast tumors, has gradually emerged as a specific subgroup of breast cancers [13–15].

The biology of TPBC is unique due to crosstalk between HER2 and HR signaling. HR+ tumors are found in about three-quarters of breast cancer patients [16] while HER2 positivity is present in approximately 15–20% of cases. Approximately half of HER2+ breast cancers are therefore HR-positive as well [17].

Both preclinical and clinical data have demonstrated that ER+ and HER2+ tumors are characterized by strong interactions between signaling pathways stimulated by estrogens and HER2 receptors. This crosstalk might result in a decrease in the efficacy of hormone therapy relative to ER+ and HER2-negative tumors. Moreover, ER positivity in HER2-overexpressing tumors can lead to resistance to anti-HER2 therapies [18–22]. In addition, there is a lack of evidence for selecting an optimal treatment strategy because patients with HER2+ tumors are usually excluded from studies evaluating endocrine therapy. An optimal combination of hormone therapy, chemotherapy, and anti-HER2 therapy has yet to be found. According to the standard treatment procedure applied in the Czech Republic, TPBC is treated with combination therapy based on standard anti-HER2 therapy, hormone therapy, and cytotoxic chemotherapy as well [23–25].

The aim of the present study was to analyze prognostic factors and outcomes in a cohort of breast cancer patients treated with anti-HER2 therapy, comparing patients with positive versus negative hormone receptor status.

Patients and methods

Patients. The BREAST research database was used as the data source for this retrospective analysis. The database contains real-world epidemiological and clinical data on breast cancer patients treated with targeted therapies, including information on histology, staging, and treatment. The database is updated twice a year and covers approximately 95% of breast cancer patients treated with targeted therapies in the Czech Republic. The database has been approved by institutional boards of the participating comprehensive cancer centers.

The analysis included data of all patients who, as of January 8, 2018, had a valid record in the BREAST research database (a non-interventional post-authorization database focused on the collection of epidemiological and clinical data on breast cancer patients) and who were treated with targeted therapies in the Czech Republic since 2011. Further inclusion criteria included the availability of data on HER2, ER, and PR status, and anti-HER2 therapy. HER2 status, hormone dependence, and grades of tumors were determined in several local laboratories. The diagram of patient selection is shown in Figure 1.

The HER2 status was tested immunohistochemically in pathology laboratories where the primary histological diagnosis was made. All cases diagnosed locally were sent to one of the so-called reference laboratories (usually within comprehensive cancer centers), where the HER2 status was confirmed by CE-IVD certified immunohistochemical tests. Cases with confirmed 3+ positivity were regarded as positive. Cases with 2+ positivity were subsequently confirmed by *in situ* hybridization – of these cases, only those with amplification of the c-erb-B2 gene were regarded as HER2-positive.

The hormone receptor status was diagnosed immunohistochemically. Because the cohort was recruited over a relatively long period of time, the cut-off values for tumors to be designated as ER/PR positive have changed; therefore, different values ranging between 1% and 10% were used as threshold criteria. In other words, all cases included in the TPBC cohort showed at least 1% expression of ER or PR. The

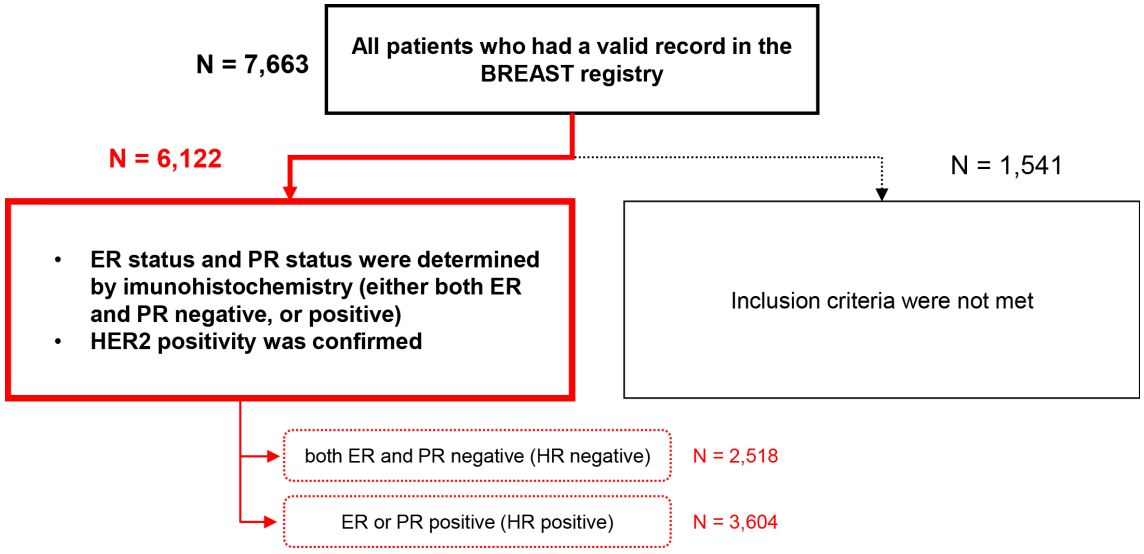

Figure 1. Analysis flowchart.

analysis included data on patients who were administered trastuzumab in the adjuvant setting, neoadjuvant setting or to treat an advanced stage of the disease. Anti-HER2 therapy was administered to patients with HER2-positive tumors unless contraindicated.

Chemotherapy and/or radiotherapy were given to patients at the physician's discretion. Likewise, patients with hormone receptor positive tumors were or were not treated with endocrine therapy at the physician's discretion. Trastuzumab combined with chemotherapy was administered in the neoadjuvant setting and in the adjuvant setting. As for patients treated with palliative intent, trastuzumab was administered in combination with either chemotherapy or endocrine therapy. The use of oral contraceptives was strictly contraindicated.

Statistical analysis. Categorical variables were described by absolute frequencies and percentages, whereas continuous variables were described by median and range. The significance of differences between subgroups of patients was examined using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.

The survival analysis was performed using the Kaplan-Meier method, with 95% confidence intervals provided for all point estimates. The overall survival was calculated from the date of diagnosis to the date of death. Surviving patients were censored on the date of the last record update in the database. Survival rates of patient subgroups were compared using the log-rank test.

All statistical tests were performed at the significance level α=0.05 using SPSS 25.0.0.1 (IBM Corporation, 2018) and R version 3.5.3 with the ggplot2 library.

Results

Patient characteristics by the presence of hormone receptors – risk factors. Overall, the analysis included data on 6,122 HER2+ patients with valid records in the BREAST research database, who were divided into two groups based on ER and PR positivity of their tumors: a) both ER and PR negative (HR negative; n=2,518), b) ER or PR positive (HR positive; n=3,604).

Patient characteristics are provided in Table 1. Table 2 describes the setting in which the first anti-HER2 therapy was administered.

Statistically significant differences were found in the age, menopausal status at diagnosis, histological type of the carcinoma, the grade of the primary tumor, stage at diagnosis, a performance status at the start of trastuzumab therapy. HR+ patients were more commonly premenopausal, diagnosed at stage I or II. HR– tumors were more commonly poorly differentiated. However, some of the statistically significant differences may have only a small clinical impact.

Overall survival. On the last follow-up update, a total of n=1,773 (70.4%) and n=2,895 (80.3%) patients were alive, with a median follow-up of 3.6 years and 3.5 years in the HR–

Table 1. Basic patient characteristics.

	HR negative (n=2,518)	HR positive (n=3,604)	p-value*
Age at diagnosis (years)			
median (range)	57 (20-88)	55 (23-85)	**<0.001**
Age at diagnosis, n (%)			
≤35 years	135 (5.4)	240 (6.7)	
35–45 years	328 (13.0)	628 (17.4)	
45–60 years	1,057 (42.0)	1,416 (39.3)	**<0.001**
60–75 years	901 (35.8)	1,206 (33.5)	
≥75 years	97 (3.9)	114 (3.2)	
Menopausal status at diagnosis, n (%)			
premenopausal	725 (28.8)	1,371 (38.0)	**<0.001**
postmenopausal	1,792 (71.2)	2,233 (62.0)	
NA	1	0	
Affected breast, n (%)			
right	1,129 (48.0)	1,656 (47.3)	
left	1,188 (50.5)	1,761 (50.3)	0.136
bilateral	37 (1.6)	81 (2.3)	
NA	164	106	
Histological type of the carcinoma, n (%)			
ductal	2,296 (91.4)	3,198 (89.0)	
lobular	59 (2.3)	204 (5.7)	**<0.001**
mixed	28 (1.1)	66 (1.8)	
other	130 (5.2)	124 (3.5)	
NA	5	12	
Grade of the primary tumor, n (%)			
1	56 (2.5)	179 (5.3)	
2	787 (34.7)	1,709 (50.3)	**<0.001**
3	1,425 (62.8)	1,507 (44.4)	
NA	250	209	
Stage at diagnosis, n (%)			
I	512 (21.2)	900 (25.8)	
II	986 (40.8)	1,601 (45.9)	**<0.001**
III	650 (26.9)	729 (20.9)	
IV	258 (10.7)	247 (7.1)	
NA	101	114	
Performance status (PS) at start of trastuzumab therapy, n (%)			
PS 0	1,282 (72.1)	2,225 (77.0)	
PS 1	469 (26.4)	625 (21.6)	**<0.001**
PS 2 or PS 3	27 (1.5)	41 (1.4)	
NA	740	713	

*Fisher's exact test or Mann-Whitney test; NA not available

Table 2. Setting of the first targeted therapy.

Setting of the first targeted therapy n (%)	HR negative (n=2,518)	HR positive (n=3,604)
trastuzumab	2,444 (97.1%)	3519 (97.6%)
neoadjuvant	444 (17.6%)	677 (18.8%)
adjuvant	1,443 (57.3%)	2314 (64.2%)
advanced/metastatic disease	557 (22.1%)	528 (14.7%)
experimental treatment	74 (2.9%)	85 (2.4%)

Experimental treatment denotes therapy within a clinical trial that has not been adopted as the standard.

and HR+ subgroups, respectively. One-, three-, and five-year OS as well as the median OS and hazard ratios within grade and stage categories are presented in Table 3. During the initial five years after diagnosis, the OS was significantly higher in HR+ patients (Figure 2).

The overall survival rate was also significantly higher in HR+ patients stratified according to treatment setting (neoadjuvant, adjuvant, and advanced/metastatic disease, Figure 3).

Comparing subgroups of patients according to tumor stage, the results showed a higher OS in HR+ patients diagnosed in stages II, III, and IV, but not in stage I (Figure 4).

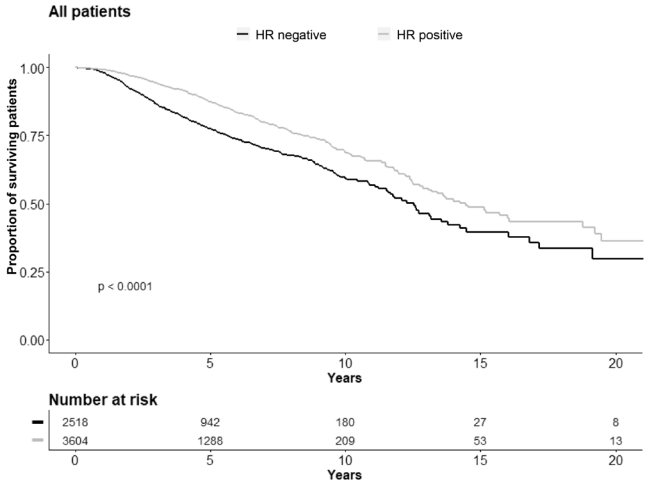

Figure 2. Overall survival.

Table 3. Overall survival (OS) from the diagnosis according to patient groups.

	HR negative (n=2,518)	HR positive (n=3,604)	p-value*
Median OS (95% CI)	12.5 years (11.5–13.5)	14.5 years (12.7–16.2)	
1-year OS (%; 95% CI)	98.2 (97.7–98.8)	99.3 (99.0–99.6)	**<0.001**
3-year OS (%; 95% CI)	86.6 (85.1–88.2)	94.2 (93.3–95.1)	
5-year OS (%; 95% CI)	77.4 (75.3–79.4)	87.3 (85.9–88.8)	
Stratification	**Hazard ratio (95% CI) for HR positive vs. HR negative**		**p-value#**
Grade			
1	0.370 (0.156; 0.877)		**0.024**
2	0.503 (0.401; 0.631)		**<0.001**
3	0.800 (0.667; 0.961)		**0.017**
Stage			
0+I	0.711 (0.463; 1.091)		0.118
II	0.714 (0.569; 0.895)		**0.003**
III	0.631 (0.510; 0.779)		**<0.001**
IV	0.614 (0.474; 0.793)		**<0.001**

*Log-rank test. #Cox proportional hazards model.

Furthermore, significantly better OS was found in patients with HR+ tumors and tumor grades 1, 2, and 3 across the entire cohort (Figure 5).

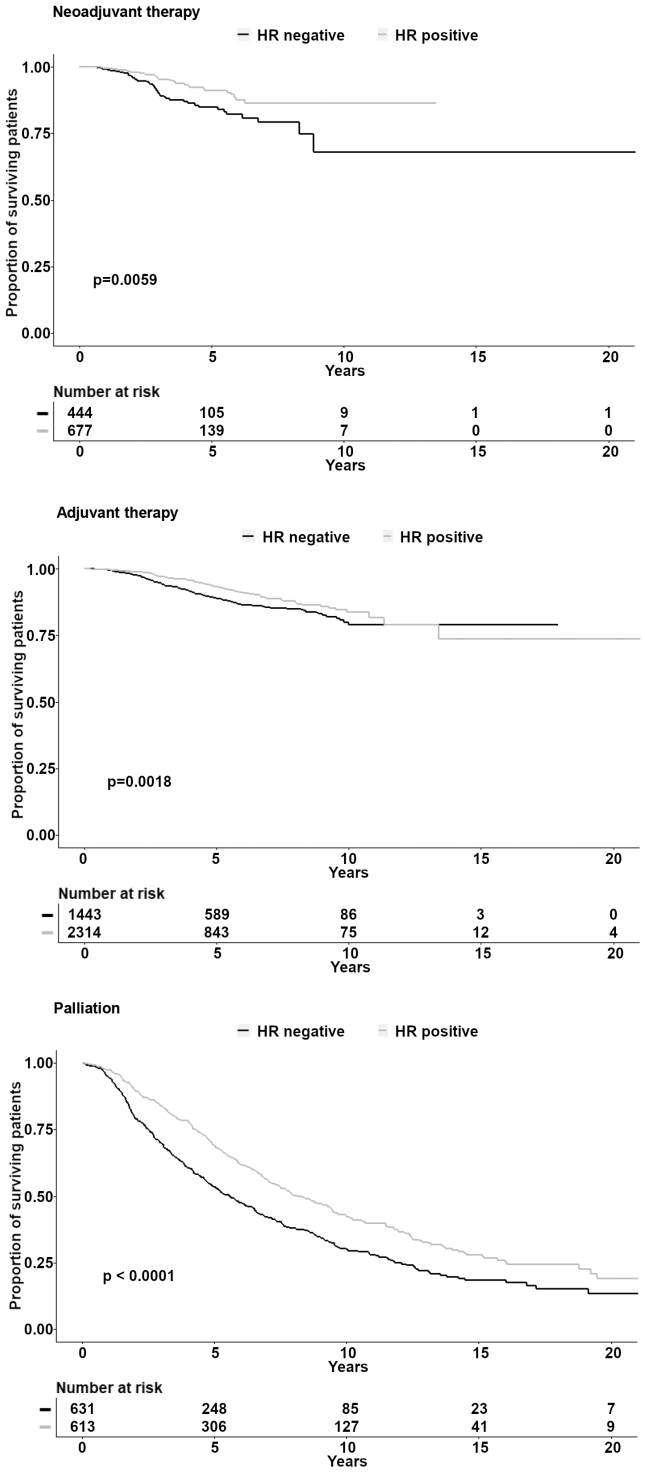

Figure 3. Overall survival according to treatment.

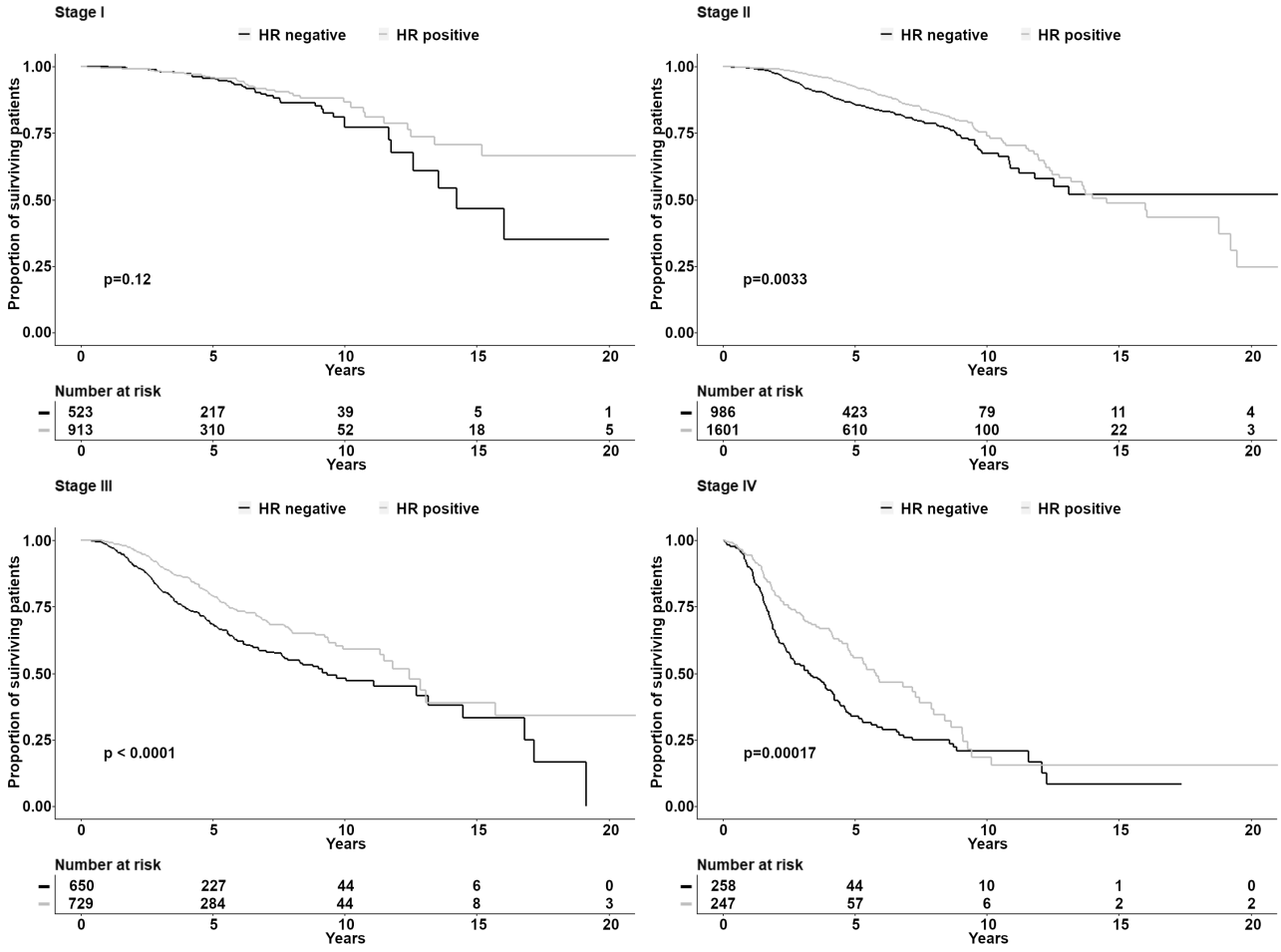

Figure 4. Overall survival according to stage.

When evaluating the effect of grade in different stages of the disease, no difference was found for grades 1, 2, and 3 in HR+ patients diagnosed at stage I (Figure 6), and a significantly higher OS was only found for grade 2 in HR+ patients diagnosed at stage II (Figure 7). After the combination of stages III and IV, a significantly higher OS was found for grades 1, 2, and 3 in HR+ patients (Figure 8).

Discussion

The results of the present retrospective analysis indicate a significantly higher OS in patients with HR+ tumors across the entire patient cohort. This effect, however, can only be evaluated with regard to the relatively short median follow-up, i.e. the first several years after the diagnosis.

We revealed the influence of HR positivity on the overall survival of patients diagnosed at stage II, III, and IV; on top of that, a higher OS was found for grade 2 in HR+ patients diagnosed at stage II. After the combination of subgroups III and IV, a higher OS was found for HR+ patients diagnosed with tumors in all grades (1, 2, and 3).

According to the literature, the pattern of relapses over time is different for TPBC and HER2+/HR– tumors. In the first five years, relapses occur more frequently in HR– tumors, whereas HR+ tumors relapse more frequently between 5 and 10 years after diagnosis [26].

A retrospective analysis of TPBC patients treated with chemotherapy alone or in combination with trastuzumab, as reported by Vici et al., demonstrated a significant effect of HR expression in the adjuvant setting [22]. Although trastuzumab was found to improve relapse-free survival (RFS) and breast-cancer specific survival in all subsets analyzed, OS differences did not reach statistical significance in the subgroup of patients with tumors containing more than 30% of hormone-dependent cells (HR>30%), and the lack of significant difference was even more apparent in patients with tumors characterized by HR expression in more than 50% of cells (HR>50%). The dynamic of relapses was markedly different in the HR > 50% group, with a low risk of relapse in the first five years after diagnosis [22]. A multivariate analysis of RFS confirmed a significant interaction between ER expression and trastuzumab efficacy, with

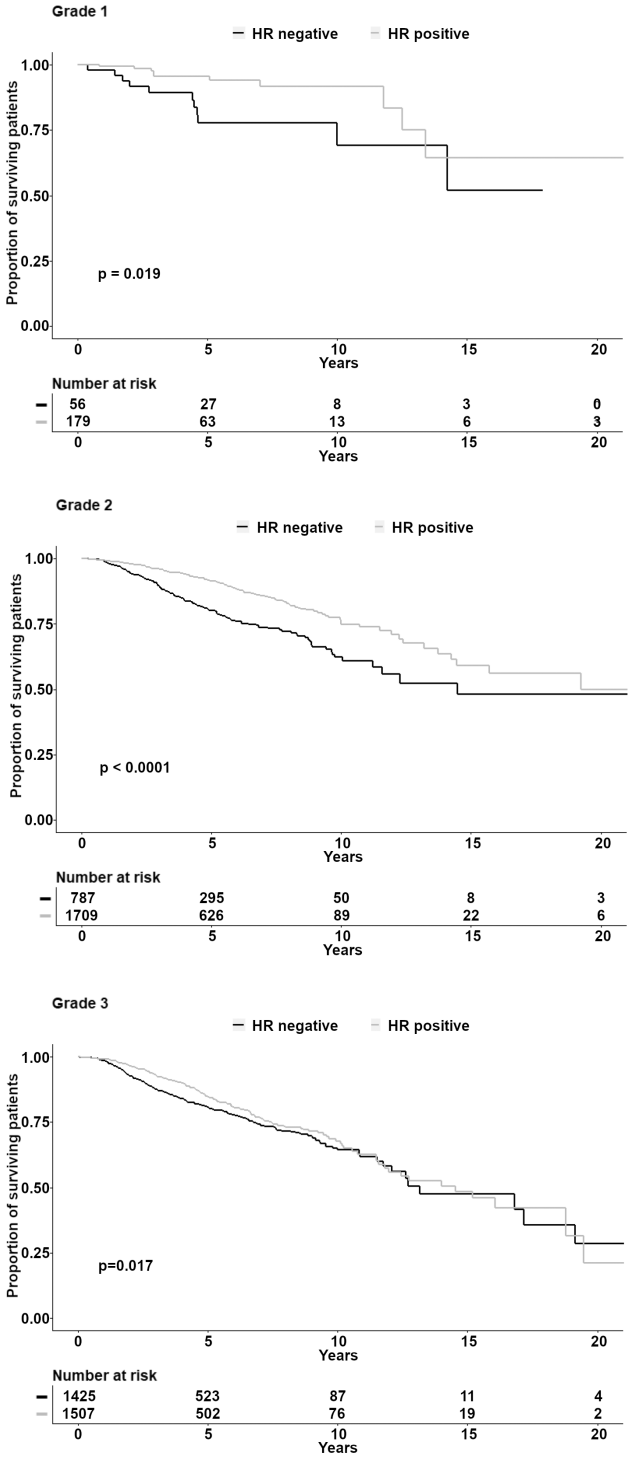

Figure 5. Overall survival according to grade.

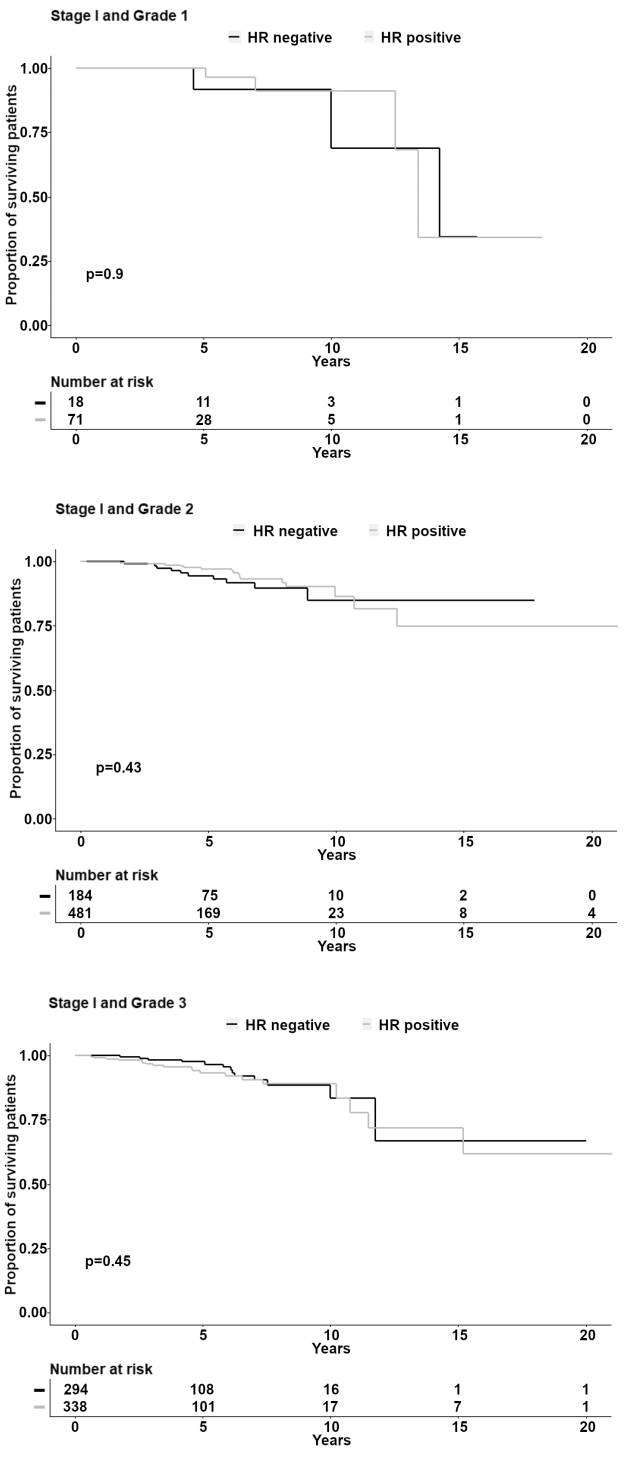

Figure 6. Overall survival according to stage I and grade 1–3.

the benefit of trastuzumab treatment confined to patients with tumors expressing ER in ≤50% of tumor cells [22]. Therefore, a question arises whether patients with highly hormone-dependent tumors have any meaningful benefit from anti-HER2 therapy.

A prospective study evaluating the effect of HR status in 3,394 patients with stage I to III HER2+ breast cancer treated in the US National Comprehensive Cancer Network centers demonstrated that patients with HR–/HER2+ disease had a significantly increased hazard of early but

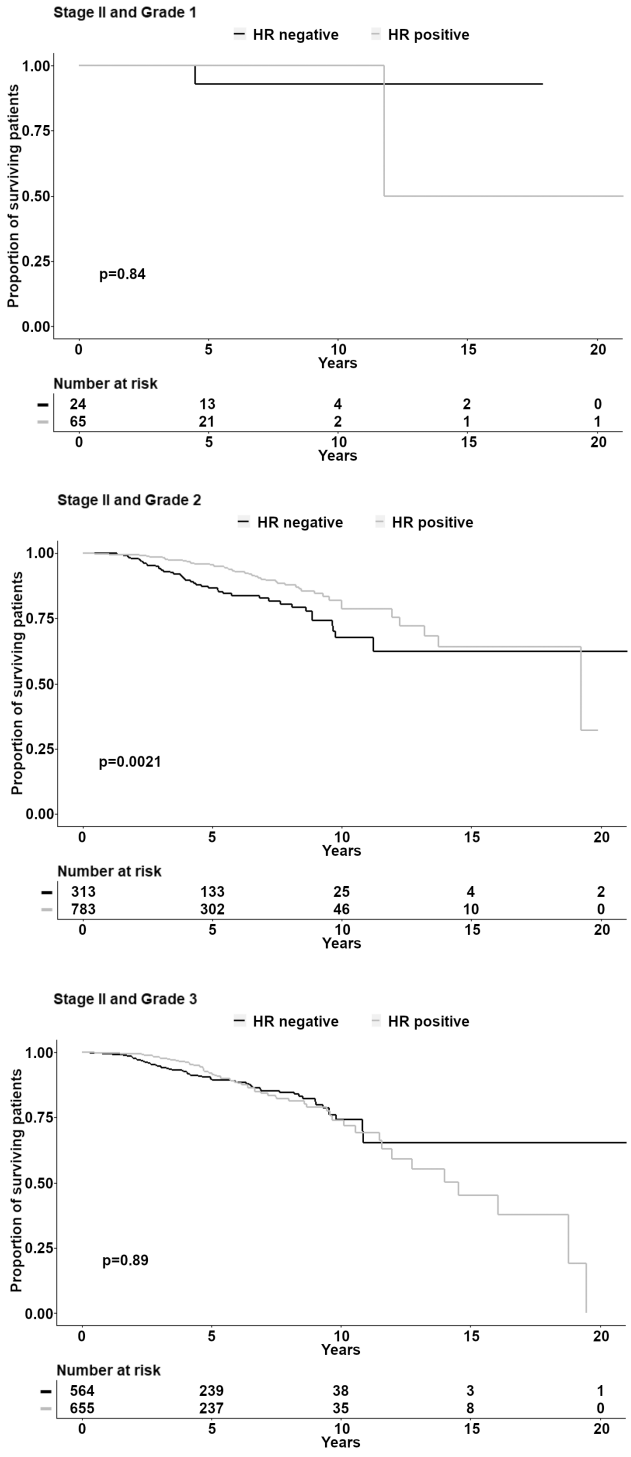

Figure 7. Overall survival according to stage II and grade 1–3.

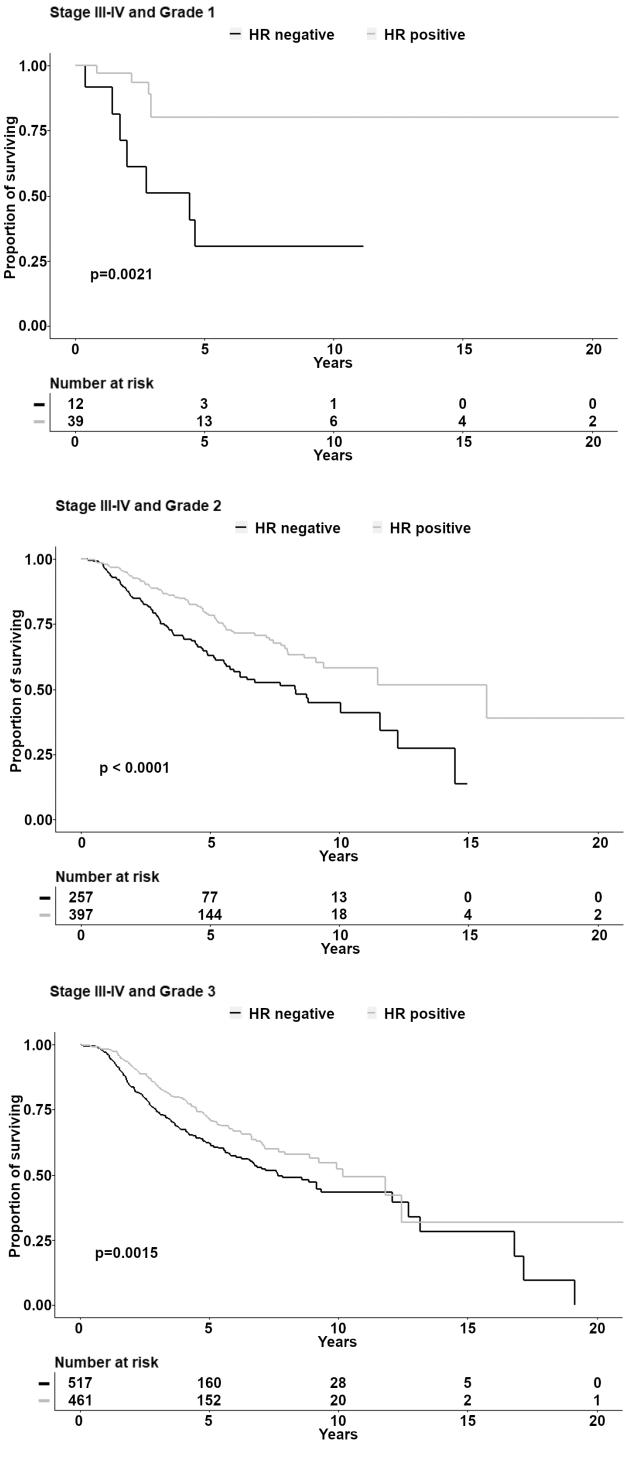

Figure 8. Overall survival according to stage III–IV and grade 1–3.

not late death when compared to TPBC patients These data suggest that the dynamics of relapse rate in TPBC with a high proportion of HR+ cells is similar to relapse curves observed in luminal HR+/HER2–negative breast cancers [9, 26, 27].

It cannot be therefore ruled out that some ER+ tumors, particularly those with a high HR positivity, show biological behavior that is similar to that of luminal tumors characterized by a relatively high frequency of late relapses. From the clinical point of view, TPBCs have many specifics that have

to be taken into consideration in neoadjuvant therapy. In general, ER+ tumor might respond less to cytotoxic therapy. The prognostic significance of pathological complete response after neoadjuvant therapy as a prognostic factor is less reliable in TPBC compared to HER2+/HR– tumors. The pathological complete response has been observed to be achieved less frequently in HER2+/HR+ tumors, regardless of long-term treatment results [28–30]. In the cohort involved in our study, the OS remained higher in patients with hormone-dependent tumors.

The question is how endocrine, cytotoxic, and anti-HER2 therapies should be optimally used in the management of TPBC in the neoadjuvant setting. Dual inhibition in neoadjuvant therapy is currently being explored. The GeparQuinto trial demonstrated that in patients with HR+ tumors, prolonged anti-HER2 therapy (neoadjuvant lapatinib for 6 months, followed by adjuvant trastuzumab for 12 months) significantly improved OS compared with anti-HER2 therapy with trastuzumab alone. A possible explanation for the benefit observed in TPBC patients in the GeparQuinto study could be the higher risk of late recurrence in these patients as well as the crosstalk of HER2 and hormone receptor signaling, which decreases the efficacy of targeted therapy. Therefore, neoadjuvant therapy with the dual EGFR/HER2 inhibitor lapatinib, followed by adjuvant therapy with trastuzumab, might result in more effective inhibition of the growth signaling, potentially rendering cells more endocrine responsive, resulting in better survival rates in TPBC patients [31, 32].

Only a limited number of studies have investigated the outcomes in advanced/ metastatic TPBC. In the present study, we observed a significantly higher OS in patients with HR+/HER2+ tumors, as compared to patients with hormone independent HER2+ tumors who were diagnosed at stage III and IV. This is in agreement with the study by Howlader et al. [33], which reported the highest survival rates in TPBC patients diagnosed at stage IV even in comparison with HR+/HER2– breast cancer, which is generally associated with the best prognosis.

The TANDEM, EGF30008, and eLEcTRA trials showed that adding anti-HER2 therapy to endocrine therapy prolongs progression-free survival (PFS) significantly, although the improvement of OS was not statistically significant [34–37].

A combination of anti-HER2 therapy and hormonal agents is therefore considered to represent an acceptable option for postmenopausal patients in whom chemotherapy is considered not feasible. Adding lapatinib to letrozole improves PFS significantly (although at the cost of higher skin toxicity and gastrointestinal toxicity), and adding trastuzumab to anastrozole was proved to prolong PFS [38].

Other retrospective analyses have suggested that adding hormone agents to anti-HER2 therapy and chemotherapy might improve treatment outcomes [39]. This has been translated into the current guidelines by both the American Society of Clinical Oncology and the European Society for Medical Oncology, which consider adding endocrine therapies to be justified as the maintenance after chemotherapy in TPBC patients in the metastatic setting [24, 40].

A number of trials have explored potential approaches to increase the treatment efficacy in TPBC patients. In the PERTAIN trial, addition of pertuzumab to the combination of trastuzumab and aromatase inhibitor after induction chemotherapy given at the investigator discretion in patients with metastatic TPBC resulted in prolongation of median PFS by 3 months [41]. The dual blockade was also investigated in the ALTERNATIVE trial [42] that enrolled patients who had prior treatment with endocrine therapy and disease progression during or after a regimen containing trastuzumab plus chemotherapy in the (neo)adjuvant setting and/or in the first-line metastatic setting.

The ALTERNATIVE trial reached its primary objective demonstrating improvement in PFS by adding lapatinib to aromatase inhibitor (AI) and trastuzumab compared to AI and trastuzumab alone [38]. The median PFS in the LAP + TRAS + AI arm was 11 months, which is comparable to results of dual inhibition combined with chemotherapy, as observed in the EMILIA or PHEREXA trials [25, 43, 44].

Representativeness of the analyzed dataset represents a strong point of this study. A check of independent sources (i.e. data provided by health insurance companies) proved that this dataset covered almost 100% of all HER2+ breast cancer patients who were or had been treated in the Czech Republic. Furthermore, information on patient survival was also reliable in the analyzed data because these records had undergone double control; first in hospital information systems, and, subsequently, during the procedure of population-based processing. On the other hand, the present study has limitations in terms of the interpretation because it is a registry-based observational analysis, which cannot aim to replace the matched comparison of arms of a randomized trial. The duration of follow-up is another limitation of the present study: the follow-up period corresponds to the profile of a sample from real clinical practice, and analyses involving follow-up periods longer than 10 years could not be adequately documented, being limited by the achievable sample size. Another important limitation is represented by the reimbursement conditions for targeted therapy that strictly regulate administration of anti-HER2 agents. These restrictions are of particular importance in patients failing trastuzumab therapy and limit the use of anti-HER2 drugs with other agents.

In conclusion, results of the present study indicate that patients with HER2+/HR+ tumors, as compared to patients with HER2+/HR– tumors, tend to present at an earlier disease stage, with lower tumor grades and are more frequently premenopausal at the time of diagnosis. In the first five years after diagnosis, the OS is significantly higher in all subgroups of HR+ patients classified by treatment setting, i.e. those treated with neoadjuvant, adjuvant, and

palliative therapy. When evaluated by stages, significantly higher OS was observed in HR+ patients diagnosed at stages II, III, and IV. We can conclude that we found an OS benefit in patients with HER2+ and HR+ tumors when compared to patients with HER2+ and HR– tumors. This difference was partly caused by differences in the presence of prognostic parameters in both groups, partly obviously by differences in their biological behavior. Although the results of our study are limited by common biases, which are caused by the design of a non-interventional database focused on the collection of epidemiological and clinical data, we consider the differences in the overall survival of both groups to be significant.

Trastuzumab became the first therapy targeting HER2. The unprecedented success of trastuzumab paved the way for the introduction of other HER2 targeted therapies, including other monoclonal antibodies (pertuzumab), dual tyrosine kinase inhibitors (lapatinib and neratinib), and antibody conjugates (e.g. trastuzumabemtansine or TDM-1). The medical therapy of HER2-positive breast cancer is mostly based on concomitant or sequential combinations of HER2-targeting agents with cytotoxic or hormonal drugs.

Mutual interactions between HER2 and hormone receptor pathways in TPBC resulted in a lot of ambiguity, and the optimal utilization of chemotherapy, hormonal treatment, and anti-HER2 therapy in treatment management has yet to be defined. According to guidelines currently used in the Czech Republic, anti-HER2 therapy should be continued after the failure of first-line treatment. In patients with HR+ tumors, after the initial anti-HER2 treatment with chemotherapy, when the response is achieved, the maintenance therapy can be continued as a combination of anti-HER2 treatment and endocrine therapy.

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