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Pathologic response rates in HER2-low versus HER2-zero early breast cancer patients receiving neoadjuvant therapy: a systematic review and meta-analysis

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Abstract

Background Currently, the primary methods for detecting HER2 expression levels are immunohistochemistry (IHC) and in situ hybridization (ISH), with the traditional standard being a HER2-positive score of 3 + accompanied by ERBB2 gene amplification detected through ISH. However, a new entity has recently emerged: HER2-low, defined as HER2 IHC 1 + or 2 + with negative ISH. HER2-low breast cancer, representing 45–60% of all HER2-negative tumors, has distinct biological characteristics and uncertain responses to conventional HER2-targeted therapies. Recent studies suggest varied clinical outcomes, highlighting the need for further investigation into the impact of HER2-low status on treatment efficacy and prognosis.

Objective This meta-analysis evaluates the difference in complete pathological response (pCR), disease-free survival (DFS), and overall survival (OS) between HER2-low and HER2-zero phenotypes.

Methods We systematically searched the main databases PubMed, Scopus, and Web of Science for articles evaluating women in neoadjuvant therapy expressing HER2-low and HER2-zero. We computed odds ratios (ORs) or hazard ratios (HRs) using DerSimonian and Laird random-effect models for all endpoints, with 95% confidence intervals (CIs). We assessed the heterogeneity using I^2 statistics. R, version 4.2.3, was used for statistical analyses.

Results 38 studies totaling 70,104 patients were included. The HER2-low group accounted for 61.3% of patients while HR + status represented 52.4% in the whole research. In 67,839 women, the pCR was analyzed, which in the overall cohort analysis favored the HER2-zero group (OR 0.84; 95% CI 0.78–0.90; $p = 0.000005$; $I^2 = 15\%$). Subgroup analyses for triple-negative breast cancer (TNBC) and HR + patients also favored HER2-zero expression, with an OR of 0.91 (95% CI 0.83–1.0; $p < 0.041$; $I^2 = 12\%$) and 0.75 (95% CI 0.70–0.81; $p < 0.000001$; $I^2 = 0\%$), respectively. In the multivariate analysis across all patients, both DFS and OS outcomes were significantly favorable for the HER2-low expression group, with HR 0.8317 (95% CI 0.7036–0.9832; $p = 0.031$) for DFS and HR 0.806 (95% CI 0.663–0.979; $p = 0.03$) for OS.

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Conclusion Based on our findings, HER2-zero status is associated with a significantly higher pathological complete response (pCR) rate compared to HER2-low in early-stage breast cancer, and other survival outcomes. These results suggest that HER2-zero should be considered a prognostic factor in early-stage breast cancer and taken into account in neoadjuvant treatment planning and future clinical research.

Keywords Breast cancer, Neoadjuvant, Pathological complete response, HER2

Introduction

Patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) have been defined for more than 20 years, represent 15–20% of all BC cases, and exhibit aggressive biological behavior and an unfavorable prognosis [1–3]. The development of anti-HER2 agents has led to drastic changes in the disease's progression, resulting in increased favorable outcomes for HER2-positive patients [4, 5]. The main predictor of response to treatment is HER2 positivity, quantified by immunohistochemistry (IHC) 3 + or in situ hybridization (ISH) (HER2 copies ≥ 6 or a HER2/CEP17 ratio ≥ 2.0) [6].

However, a new classification entity has recently emerged, termed BC HER2-low, representing 45–60% of all HER2-negative tumors [7–9]. Patients in this category do not seem to benefit from conventional HER2-targeted therapies such as trastuzumab and pertuzumab [5, 10, 11]. However, antibody–drug conjugates (ADCs) like trastuzumab deruxecan (T-DXd) and trastuzumab duocarmazine (SYD985) show potential antitumor activity in HER2-low patients, garnering significant attention for this emerging subgroup [12–14].

Different studies suggest that HER2-low and HER2-zero (negative) cancers have distinct biological, histological characteristics, and proliferation rates [15, 16]. However, the impact of HER2-low expression on chemotherapy response and survival in early-stage patients remains controversial [6]. Previous studies have reported that HER2-low patients do not seem to have a distinct prognostic value regarding pathological complete response (pCR) and survival following neoadjuvant chemotherapy (NAC) [17, 18]. Conversely, an analysis conducted by Denkert et al. involving 2310 patients from four prospective neoadjuvant clinical trials revealed a significant difference in the HER2-low subgroup, which had a lower pCR rate and higher survival compared to HER2-zero patients [19]. These differences in clinical outcomes may reflect the significant variations between the populations included in each study. Thus, further research is essential to elucidate the influence of HER2 status on pCR, which currently represents an unmet medical need.

In recent years, the role of NAC has evolved dramatically, although residual disease after this treatment increases the risk of recurrence or death. Yet, the influence of HER2-low status on the clinical efficacy of NAC has not been fully elucidated. Therefore, we conducted a systematic review and meta-analysis to clarify the impact of HER2-low compared to HER2-zero on pCR in patients treated with NAC.

Methods

Protocol and registration

We conducted this systematic review and meta-analysis in strict accordance with the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[20] and the Cochrane Handbook for Systematic Reviews of Interventions [21]. Our protocol was pre-registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42024558430. The complete PRISMA Checklists are detailed in Tables S1 and S2, Supplementary Materials.

Our meta-analysis included studies that followed the following PICOTT question: *Population*—patients with early breast cancer receiving neoadjuvant therapy; *Intervention*—patients expressing HER2-low molecular type; *Control*—patients expressing HER2-zero molecular type; *Outcomes*—to evaluate the pathological complete response (pCR), disease-free survival (DFS), and overall survival (OS). Thus, we sought to answer the following question: is the expression of HER2-low vs HER2-zero associated with the best pCR, DFS, and OS rates?

Eligibility criteria

Studies that met the following eligibility criteria were included: (1) observational, case–control, and cohort studies; (2) enrolling patients who underwent neoadjuvant therapy; (3) patients ≥ 18 years of age with early (non-metastatic) breast cancer; (4) comparative prognostic analysis between HER2-zero (IHC score 0) and HER2-low (IHC 1 + or 2 + and ISH/FISH negative) expression levels. We excluded studies with overlapping populations, randomized clinical trials, no outcomes of interest, and studies that did not specify the type of HER2 expression.

Search strategy

The studies included in this investigation were systematically searched in the Pubmed, Scopus, and Web of Science databases on June 15, 2024. No publication limits were applied. In the search strategy we combined the

following related terms and their related MeSH variations using the Boolean operators (AND/OR): "Breast Cancer", "HER2", "Neoajudvant", "low", "zero". The complete search strategy with the MeSH terms is detailed in Table S3, Supplementary Material. Those found in the databases and the references of the articles were incorporated into the reference management software (EndNote®, version X7, Thomson Reuters, Philadelphia, USA). Duplicate articles were automatically and manually excluded. Titles and abstracts of articles found in the databases were analyzed independently by two reviewers (C.H.D.C.R. and F.D.D.L.P.). Disagreements were resolved by consensus between two authors and the senior author, a third reviewer (C.H.D.C.R., F.D.D.L.P., and F.C.A.M.).

Data extraction

Two authors (C.H.D.C.R. and F.D.D.L.P.) extracted data of the following patient characteristics reported in the studies: number of patients with HER2-low or HER2-zero; follow-up; age; menopausal status; HR status; histology; clinical T-stage; clinical N-stage; TNM stage; Ki-67. The ensuing outcomes of interest were extracted: Pathological complete response (PCR), defined as the absence of cancer in the breast surgical tissue specimens post-neoadjuvant therapy; Overall survival (OS), defined as the time from the start of treatment that patients are still alive; Disease-free survival (DFS) or recurrence-free survival (RFS), defined as the period after successful treatment in which there is no relapse of the disease. All endpoint definitions are consistent with the Standardized Definitions for Efficacy End Points (STEEP) criteria for breast cancer studies [22, 23]. For publications reporting results from the same study, the most recent or complete publication reporting relevant details for our analysis was considered.

Risk of bias assessment

The risk of biases was conducted individually among the three authors (F.D.D.L.P., C.H.D.C.R., and F.C.A.M.) and disagreements were resolved by consensus. To ensure the quality of the assessment, observational studies were analyzed using the Newcastle–Ottawa Scale (NOS) [24], classified as High-Quality, Moderate-Quality, or Low-Quality observational studies according to their results in three domains: Selection, Comparability, and Outcome. Funnel-plot analyses were employed to examine publication bias.

Statistical analysis

The hazard ratio (HR) was used to analyze the DFS and OS. We consider HR > 1 favoring the control group HER2-zero and HR < 1 favoring the intervention group HER2-low. For survival outcomes, the following confounding factors were primarily considered in the multivariate analysis: HER2 status, age, T stage, N stage, histopathological type, grading, and hormone receptor status. The selection of these variables in the included studies was based on their statistical significance in univariate analysis (typically with a P value ≤ 0.2) or their clinical relevance. Those evaluated with binary outcomes were assessed with odds ratios (ORs), with 95% confidence intervals (CIs). The Cochrane Q-test and I^2 statistics were used to evaluate heterogeneity; P values > 0.10 and I2 values > 25% were considered to indicate significance for heterogeneity [25]. The Sidik-Jonkman estimator was used to calculate the tau2 variance between studies. We used DerSimonian and Laird random-effect models for all endpoints [26]. Publication bias was explored using Egger's linear regression test [27]. The packages used were "meta" and "metagen". Statistical analyses were performed using R statistical software, version 4.2.3 (R Foundation for Statistical Computing).

Results

Search results and characteristics of included studies

The selection process is detailed in a PRISMA flow diagram (Fig. 1). Our systematic search identified 8317 references. After removing 4304 duplicates and screening titles and abstracts for eligibility, we excluded 8238 references and assessed 79 full-text manuscripts for inclusion and exclusion criteria. Ultimately, 38 studies met the criteria and were included in the analysis, comprising 70,104 patients.

A total of 42,942 patients (61.3%) with early breast cancer expressed HER2-low, while 27,162 patients (38.7%) expressed HER2-zero. Among them, 6,683 patients (9.5%) were in the pre/perimenopausal status and 4854 in postmenopausal. The most common histological type was ductal, with 48,698 patients (69.5%). Hormone receptor status was positive in 36,750 patients (52.4%). The Clinical T-stage had 45,329 patients (64.7%) in stages cT0–cT2. The Clinical N-stage included 52,642 patients (75.1%) in stages N0-N1. Meanwhile, Clinical Stage I–II had 4611 patients (6.6%). The characteristics of the patients are summarized in Table 1.

Results based on outcome

Pathological complete response

Of the included studies [19, 23–59], 36 analyzed the pathological complete response (pCR), representing 67,839 patients. Among these women, the pCR rate significantly favored the HER2-zero phenotype (OR 0.84; 95% CI 0.78–0.90; $p < 0.000005$; $I^2 = 15\%$; Fig. 2). In the subgroup analysis, 40,121 women were HR + (hormone receptor-positive) and 27,718 were TNBC (triple-negative breast cancer). In both subgroups, the pCR rate

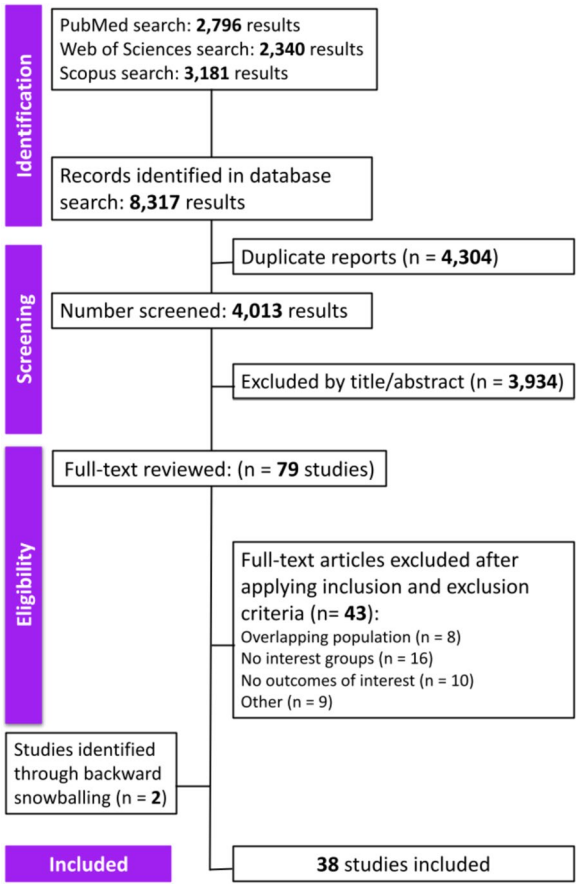

Fig. 1 PRISMA flow diagram of study screening and selection

favored the HER2-zero group. For the HR + subgroup, the results showed an OR of 0.75 (95% CI 0.70–0.81; $p < 0.000001$; $I^2 = 0\%$; Fig. 2a). For the TNBC subgroup, the results presented an OR of 0.91 (95% CI 0.83–1.0; $p < 0.041$; $I^2 = 12\%$; Fig. 2b).

Disease-free survival

Among the included studies, 16 presented analyses for DFS. In the univariate analysis, the HR + phenotype did not show statistical significance in favor of HER2-low (HR 1.005; 95% CI 0.823–1.226; $p = 0.963$). Similarly, the TNBC phenotype also did not demonstrate statistical significance in favor of HER2-zero (HR 1.209; 95% CI 0.646–2.259; $p = 0.553$). However, when considering all patients irrespective of hormone receptor status, the univariate analysis showed no significant benefit for HER2-low (HR 0.889; 95% CI 0.711–1.112; $p = 0.303$).

In the multivariate analysis, the HR + phenotype still did not show statistical significance in favor of HER2-low (HR 0.875; 95% CI 0.745–1.028; $p = 0.104$). For the TNBC phenotype, the analysis also did not demonstrate statistical significance in favor of HER2-zero (HR 0.947; 95% CI 0.676–1.326; $p = 0.751$). When considering all patients, the HER2-low group showed a significant benefit (HR 0.8317; 95% CI 0.7036–0.9832; $p = 0.031$). All data is available in Table 2.

Overall survival

Seventeen studies reported data for OS. The univariate analysis for the HR + phenotype did not indicate a significant benefit for the HER2-low group (HR 0.919; 95% CI 0.751–1.126; $p = 0.416$). In the same way, for the TNBC phenotype, the results showed no significant difference favoring HER2-zero (HR 0.987; 95% CI 0.732–1.330; $p = 0.931$). When considering the entire cohort, the univariate analysis did not reveal a significant benefit for HER2-low (HR 0.798; 95% CI 0.625–1.019; $p = 0.071$).

In the multivariate analysis, the HR + phenotype exhibited a clear advantage for the HER2-low group (HR 0.825; 95% CI 0.779–0.875; $p < 0.001$). Meanwhile, for the TNBC phenotype, the data did not show a significant difference favoring HER2-zero (HR 0.945; 95% CI 0.636–1.404; $p = 0.778$). Analyzing all patients together, the multivariate results demonstrated a statistically significant improvement for those in the HER2-low group (HR 0.806; 95% CI 0.663–0.979; $p = 0.03$). All data is available in Table 2.

Sensitivity analysis

We performed a leave-one-out sensitivity analysis for all outcomes. Heterogeneity was low when analyzing the primary outcome of pCR ($I^2 < 25\%$). However, our analysis showed increased heterogeneity in the outcomes of OS ($I^2 = 63\%$) and DFS ($I^2 = 61\%$) in both univariate and multivariate analyses. Despite performing sensitivity analyses on both OS and DFS outcomes, there were no studies that contributed asymmetrically to the results. In the GOSH plot, significant overlap between the two groups suggested low variance, with most heterogeneity concentrated on the high side, accompanied by a corresponding decrease on the low side (Fig. 3a). There was no significant variation in the stability analysis of the drapery plot in our study, an indication of the robustness of our results (Fig. 3b). The leave-one-out sensitivity and drapery plot analysis of the main results is detailed in Supplementary Figs. S1 and S5.

Estimation of publication bias

We conducted a funnel plot analysis for all outcomes (Fig. 4A). The X-axis corresponds to the odds ratio, while the Y-axis represents the standard error. The dashed lines indicate two standard errors on either side of the mean effect. Each circle is representative of one study. Additionally, Egger's test was used to statistically assess the asymmetry of the funnel plot. In the pCR analysis, the

Table 1 Characteristics of included studies

Author, year	Country	Inclusion period	Median follow-up (months)	Total number of patients (*n*)	Patients with HER2-low/HER-0 (*n*)	HR status	Clinical T stage	Clinical N stage	Stage	NOS scale
De Moura Leite et al. 2021 [28]	Brazil	2007–2018	59	855	285/570	HR + and HR −	T1–T4	N0–N3	1–3	8
Denkert et al. 2021 [19]	Europe	2012–2019	47	2310	1098/1212	HR + and HR −	T1–T4	N0–N3	1–3	8
Kang et al. 2022 [29]	Korea	2014–2018	–	1572	754/818	HR + and HR −	T1–T4	N0–N3	1–3	7
Jing-Jing Li et al. 2023 [30]	China	2017–2017	59	283	239/44	HR + and HR −	T1–T4	N0–N3	2–3	9
Qiao et al. 2023 [31]	China	2017–2021	20	132	70/62	HR + and HR −	–	–	–	7
Shao et al. 2022 [32]	China	2017–2019	–	314	226/88	HR + and HR −	T1–T4	N0–N3	2–3	7
Xu et al. 2023 [33]	China	2018–2021	24	429	267/162	HR + and HR −	T1–T4	N0–N3	2–3	9
Garufi et al. 2023 [34]	Italy	–	53	566	340/226	HR +	–	–	–	8
Pöschke et al. 2023 [35]	Germany	1998–2020	240 (20y)	1373	930/443	HR + and HR −	T1–T4	N0 − N +	1–3	7
Yang et al. 2023 [36]	China	2015–2017	–	177	117/60	HR + and HR −	T1–T4	–	–	8
Dai et al. 2023 [37]	China	2015–2016	71	55	24/21	HR + and HR −	–	–	1–3	8
Guochun Zhang et al. 2022 [38]	China	2016–2017	–	87	63/24	HR + and HR −	T1–T4	N0–N3	1–3	7
Karakas et al. 2023 [39]	USA	2020–2021	49	130	75/55	HR + and HR −	–	–	1–4	9
Ma et al. 2023 [40]	China	2015–2021	55	546	292/254	HR −	T1–T4	N0–N3	1–3	7
Miglietta et al. 2022 [41]	Italy	2002–2018	–	261	105/156	HR + and HR −	–	–	–	7
Alves et al. 2022 [42]	Portugal	2015–2020	36	72	41/31	HR + and HR −	T1–T4	N0–N3	2–3	9
Ilie et al. 2023 [18]	France	2007–2018	54 (4.5y)	511	236/275	HR + and HR −	T0–T4	N0–N3	1–3	8
Zhu et al. 2023 [43]	China	2009–2020	24	1473	1023/450	HR + and HR −	–	–	–	7
Wang et al. 2023 [44]	China	2018–2022	18	148	93/55	HR + and HR −	–	–	–	6
Toss et al. 2022 [45]	Italy	2008–2020	55	142	82/57	HR −	T1–T4	N0 − N +	–	9
Shi et al. 2023 [46]	China	2014–2022	–	430	249/181	HR + and HR −	T1–T4	N0 − N +	–	8
Nonneville et al. 2022 [47]	France	2005–2021	73	1111	456/655	HR + and HR −	T0–T4	N0 − ≥ N1	1–3	8
Huiyue Li et al. 2023 [48]	USA	2010–2018	65	45,331	28,172/17159	HR + and HR −	T1–T4	N0–N3	–	7
Domergue et al. 2022 [49]	France	2005–2020	73	437	121/316	HR −	T0–T4	N0 − ≥ N1	1–3	9
Di Cosimo et al. 2022 [50]	Italy	2009–2020	60	444	335/109	HR + and HR −	–	N0–N3	1–3	7
Shichao Zhang et al. 2023 [51]	China	2011–2022	40	3070	2340/730	HR +	–	–	–	7
Yi et al. 2023 [52]	China	2017–2020	32	86	62/24	HR + and HR −	T1–T4	N0–N3	1–3	9
Shiyuan Zhang et al. 2023 [53]	China	2011–2019	67	653	279/374	HR + and HR −	T1–T4	N0–N3	1–3	8
Reinert et al. 2021 [54]	Brazil	NA	56	331	167/164	HR + and HR −	–	–	–	7
Yijun Li et al. 2023 [55]	China	2010–2020		1027	678/349	HR + and HR −	T1–T4	N0–N3	1–3	9
Jin et al. 2023 [56]	China	2013–2019	43	693	561/132	HR + and HR −	T1–T3	N0–N3	–	9
Douganiotis et al. 2022 [57]	Grece	2007–2021	34	113	80/33	HR +	–	–	–	8

Table 1 (continued)

Author, year	Country	Inclusion period	Median follow-up (months)	Total number of patients (*n*)	Patients with HER2-low/HER-0 (*n*)	HR status	Clinical T stage	Clinical N stage	Stage	NOS scale
Djurmez et al. 2023 [58]	Serbia	2020–2021	–	75	62/13	HR + and HR –	–	–	–	8
Tarantino et al. 2024 [59]	USA	2016–2022	35 (2.94y)	991	491/500	HR + and HR –	–	N0–N3	–	9
Tang et al. 2022 [60]	China	2012–2019	–	905	685/220	HR + and HR –	T1–T4	N0–N3	–	7
Zhou et al. 2023 [61]	China	2016–2021	29.3	325	234/91	HR + and HR –	T1–T4	N0–N3	1–3	8
Shao et al. 2024 [62]	China	2017–2020	–	410	293/117	HR + and HR –	T1–T4	N0–N3	2–3	8
Tuluhong et al. 2023 [63]	China	2008–2019	72.7	246	157/89	HR + and HR –	T1–T4	N0–N3	1–3	7

HR hormone receptor; *n* number; *y* years; *NOS* Newcastle–Ottawa scale

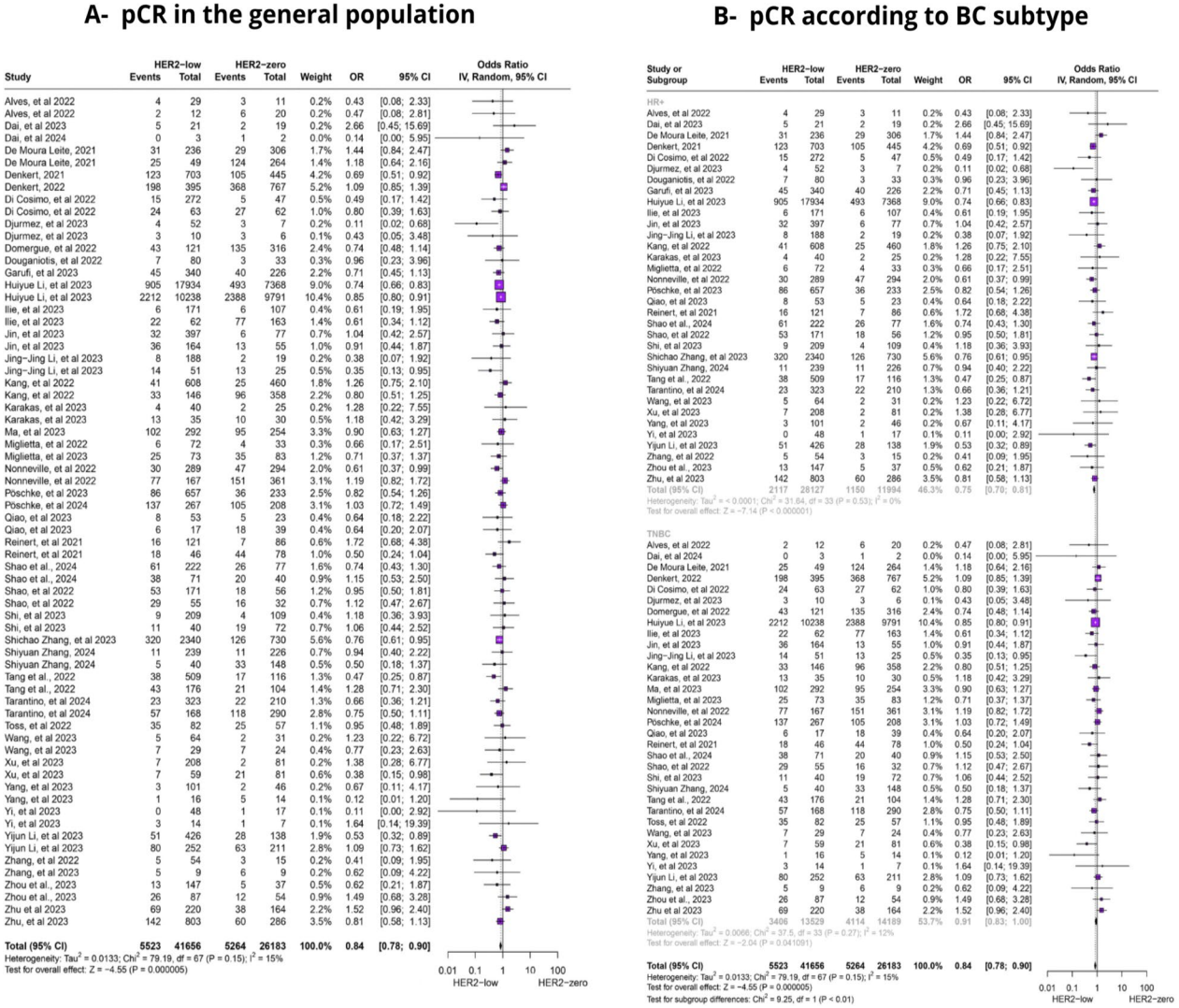

Fig. 2 Forest plot of adjusted analyses for association between HER2 expression and pathological complete response. **a** pCR of all studies; **b** pCR of HR + subgroups; **c** pCR of TNBC subgroups

funnel plot demonstrated a homogeneous distribution with a low risk of biases among most studies, except for Djumenez et al. Additionally, Egger's test for this outcome showed a *p*-value of 0.395 and a bias estimate of − 0.14 (SE = 0.17). For the univariate analysis of OS and DFS, the groups displayed minimal dispersion in the funnel plot, except for three studies that showed more extreme dispersion in both groups. Egger's test for OS indicated a *p*-value of 0.294 and a bias estimate of − 0.61 (SE = 0.55), while for DFS, it showed a *p*-value of 0.263 and a bias estimate of − 1.30 (SE = 1.1) (Fig. 4B). In the multivariate analysis, seven studies in the OS group and five studies in the DFS group were outside the funnel plot, indicating greater dispersion and potential bias. Egger's test indicated a *p*-value of 0.503 and a bias estimate of − 0.34 (SE = 0.50) for OS, and a *p*-value of 0.636 with a bias estimate of − 0.32 (SE = 0.67) for DFS. The detailed funnel plot analysis of the main outcomes can be found in Supplementary Fig. S4.

Quality assessment

The individual assessment of each observational study included in the meta-analysis is depicted in Table S5, Supplementary Material. The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS). Out of the 34 studies evaluated, 33 scored between 7 and 9 points, indicating high quality. One study, conducted by Wang et al., scored 6 points due to lower marks in ascertainment of exposure, main factor, and additional factor (Supplementary Table 4).

Table 2 Analysis of DFS and OS

Outcome	Univariate			Multivariate*		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
OS ALL**	0.7984	0.6253–1.0194	0.071	0.8061	0.6633–0.9795	0.03
OS HR +	0.9193	0.7506–1.1258	0.416	0.8255	0.7790–0.8748	< 0.001
OS TNBC	0.9869	0.7323–1.3300	0.931	0.9447	0.6356–1.4039	0.778
DFS ALL**	0.889	0.7106–1.1122	0.303	0.8317	0.7036–0.9832	0.031
DFS HR +	1.0047	0.8232–1.2262	0.963	0.8751	0.7451–1.0277	0.104
DFS TNBC	1.2086	0.6465–2.2592	0.553	0.9468	0.6758–1.3265	0.751

CI confidence interval; *DFS* disease-free survival; *HR* hazard ratio; *TNBC* triple-negative breast cancer

* Adjusted by HER2 status, age, T stage, N stage, histopathological type, grading, and hormone receptor status

** Complete OS and DFS data available in supplementary Figs. S2 and S3

Discussion

The HER2-low category has recently gained significant attention in clinical research and practice guidelines. In 2023, the European Society for Medical Oncology (ESMO) issued an expert consensus on the definition, diagnosis, and management of HER2-low breast cancer [7, 64]. Evidence from clinical trials suggests that antibody–drug conjugates may be clinically effective in tumors with low to moderate HER2 expression [65, 66]. Our meta-analysis provides insights into this potential marker in the analysis of pathological complete response (pCR) among patients with early-stage HER2-low and HER2-zero breast cancer undergoing neoadjuvant chemotherapy, and our data reinforce findings from previous meta-analyses [67, 68]. This analysis, which includes 70,104 patients from 38 studies, demonstrates that HER2-zero status is associated with superior pathological response rates, but HER2-low as well as improved overall survival and disease-free survival.

HER2-low status is more frequent in HR + patients, and HER2-low staining rates increase as HR increases. Regarding clinicopathological characteristics, in HR-negative tumors, HER2-low, when compared to HER2-zero, was significantly associated with low-grade tumors (35% vs. 18%) and in tumors with apocrine IHC markers (57% vs. 36%). Thus, these results could indicate that, in HER2-negative tumors, low HER2 expression is more often associated with favorable prognostic characteristics [69, 70]. The findings of this meta-analysis provide grounds to discuss whether HER2-zero could be a potential predictor of pathological complete response to neoadjuvant treatment in HR + and could be substantially important for informing clinical therapies—although HER2-low tumors had better survival outcomes. Our study can show the variation from HER2-low to treatment response for TNBC, however, it is important to emphasize that our data only support the current standard treatment for early TNBC, which is cytotoxic chemotherapy.

The primary outcome of interest, pCR, demonstrated a significant association favoring HER2-zero phenotype across all included studies. This finding was consistent across subgroups stratified by hormone receptor status, indicating that HER2-zero status correlates with higher rates of pCR, particularly pronounced in hormone receptor-positive breast cancer. The analysis revealed an odds ratio (OR) of 0.75 (95% CI 0.70–0.81) for HR + subgroups and 0.91 (95% CI 0.83–1.0) for triple-negative breast cancer (TNBC) subgroups. This rate difference has previously been described among patients undergoing neoadjuvant chemotherapy in Germany, where HER2-low status was associated with lower pCR for HR +, but not for HR-negative patients [19].

Previous studies have demonstrated that triple-negative breast cancer (TNBC) achieves higher pathological complete response (pCR) rates following neoadjuvant chemotherapy compared to hormone receptor-positive (HR +) breast cancer [71, 72]. The biological basis for this disparity is linked to distinct immunoreactive tumor microenvironments between the two cancer types. Specifically, TNBC tumors exhibit elevated levels of PD-L1 + cells within both the tumor and stroma, as well as higher infiltration scores of memory B-cells, activated memory CD4 + T-cells, follicular helper T-cells, and M0 and M1 macrophages, in comparison to luminal breast cancer subtypes [73].

For TNBC, neoadjuvant therapy is the standard practice [74]. In contrast, the optimal timing of neoadjuvant chemotherapy for HR + breast cancer is uncertain. This question arises in part from a concern that starting treatment with hormonal therapy may offer advantages such as reduced risk and lower toxicity. However, our results indicate that women with HR + early breast cancer experience significant benefits in terms of pathological

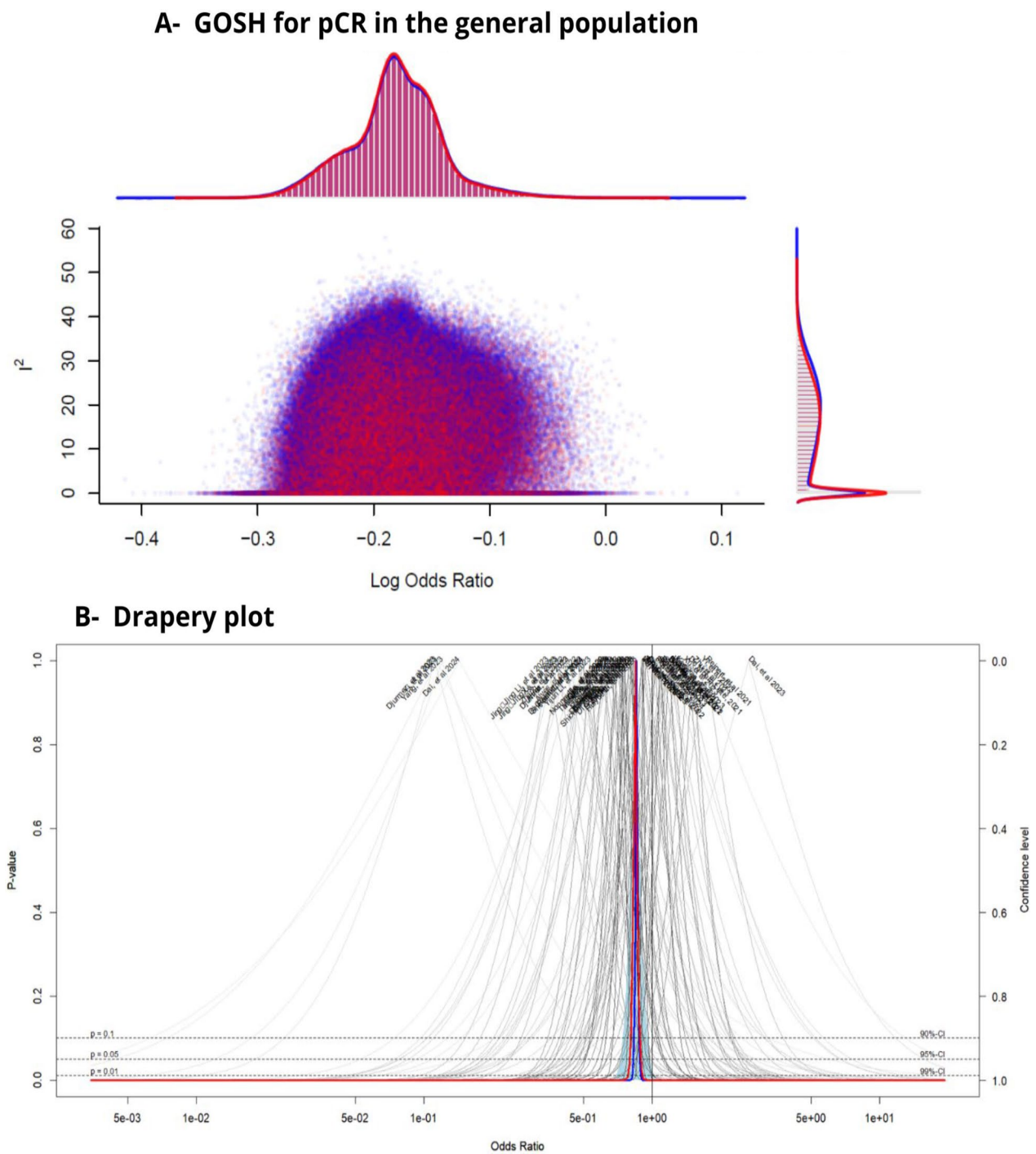

Fig. 3 Assessment of heterogeneity between studies; **A** GOSH plot analysis; **B** Drapery plot analysis

complete response, with an odds ratio of 0.088 in a cohort of 40,121 women analyzed. Within this group, patients with HER2-zero status demonstrated more pronounced benefits from pathological complete response compared to those with the HER2-low phenotype (OR 0.84; 95% CI 0.78–0.90; $p < 0.000005$; Fig. 2a). Consequently, HER2-zero could be a secondary prognostic marker in HR + tumors, guiding the decision for cytotoxic chemotherapy and being a valuable tool for personalized treatment strategies.

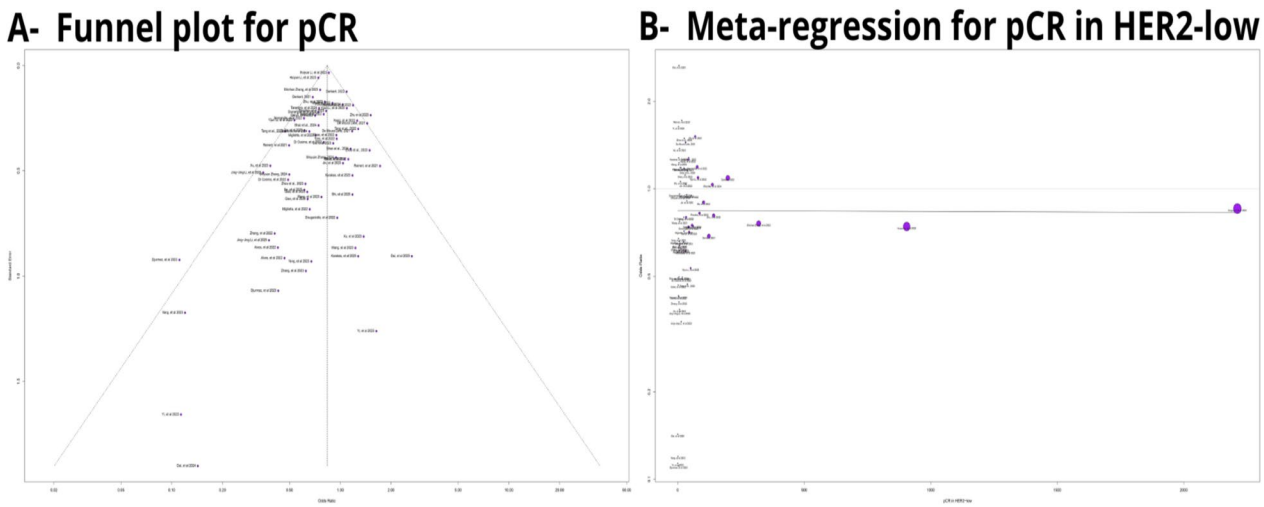

Fig. 4 Assessment of publication bias; **A** Funnel plot analysis; **B** Meta-regression analysis

Concerning overall survival, the analysis of all patients (without stratification by TNBC or HR+) revealed statistical significance only in the multivariate analysis, with a hazard ratio (HR) of 0.8061 ($p=0.03$). When evaluating the subtypes separately, no statistical significance was detected for this outcome in women with TNBC in either the univariate or multivariate analyses. In contrast, for the HR+ phenotype, the multivariate analysis demonstrated significance, with an HR of 0.8255 and a p-value of <0.001, favoring HER2-low expression over HER2-zero. Overall survival is a critical endpoint in assessing the effectiveness of treatments, particularly in early breast cancer. However, it should be interpreted with caution due to the prolonged progression from early-stage tumor to metastatic disease, which can often take several years [75]. Shorter follow-up durations may lead to the erroneous conclusion that a treatment does not confer survival benefits, thereby resulting in potentially misleading interpretations.

Regarding disease-free survival, significance was found only in the overall group, with a hazard ratio of 0.8317 and a p-value of 0.031 in the multivariate analysis, favoring the HER2-low subtype compared to HER2-zero. A study conducted in Germany, involving 2310 women with HER2-non-amplified primary breast cancer treated with neoadjuvant therapy, reported similar findings to ours. They observed significance in the disease-free survival outcome (3-year rate) favoring the HER2-low subgroup, both in the overall group and in the subset of patients with hormone receptor-negative breast cancer [19]. Furthermore, an exploratory survival analysis with approximately 10 months of median follow-up in 5235 HER2-negative patients supports most of our DFS findings. This study also did not find statistical significance when analyzing HR-positive and triple-negative breast cancer tumors separately, but it did find statistical significance in DFS for the overall group [8].

Given the pCR outcomes, our findings have significant clinical implications that support the use of HER2 as a prognostic biomarker, potentially justifying ADC therapy, particularly for HR+HER2-zero women. Additionally, we found that the group HR+, with the highest pCR, also exhibited superior overall survival and disease-free survival in a multivariate analysis, favoring the HER2-low phenotype. Prior studies have shown that pCR is a critical prognostic indicator, consistently associated with positive overall outcomes [76].

Conventionally pCR has been considered a prognostic indicator of better outcomes in breast cancer overall. However, our results reveal an interesting and distinct finding: despite the pCR rate observed in the HER2-zero group, the HER2-low group demonstrates significantly better survival. This suggests that pCR may not be the sole determinant or prognostic marker of relevance in the neoadjuvant setting. Moreover, biomarkers such as liquid biopsy, tumor-infiltrating lymphocytes, and other genetic markers could play a critical role in evaluating treatment response in a more integrated manner, as pCR alone may not fully predict survival outcomes [77, 78]. Additionally, population and ethnic differences may account for the heterogeneity observed and could potentially compromise the generalizability of our findings, despite the large population included in this meta-analysis. Furthermore, the observational nature of the included studies could limit the generalizability and statistical power of the combined analysis, as well as increase the risk of bias.

Recent advances in understanding HER2-zero status as a prognostic marker for patients undergoing neoadjuvant

treatment have highlighted its substantial importance in treatment planning. The DESTINY-Breast06 study made significant contributions to the field by exploring HER2-low/ultralow status, particularly demonstrating that treatment with trastuzumab deruxtecan provided significant benefits in 866 patients with metastatic breast cancer (713 HER2-low and 153 HER2-ultralow), with improved PFS (HR 0.62; $P<0.001$), showing consistent results in the HER2-ultralow population [79]. These findings suggest that this treatment option should be considered in the development of personalized clinical protocols, and HER2 classification could guide the individualization of breast cancer treatment in the neoadjuvant setting.

For the limitations of our study, it is essential to acknowledge that our meta-analysis is primarily composed of observational studies. Also, we identified significant heterogeneity in the disease-free survival outcomes for TNBC and the overall group, in both univariate and multivariate analyses. Similarly, we observed considerable heterogeneity in the overall survival outcomes across all univariate and multivariate analyses. Nevertheless, sensitivity analyses and meta-regression indicated that our data follow a linear trend, suggesting a closer alignment with the true effect and a high level of reliability in the association between the HER2-zero phenotype and pathological complete response. We utilized leave-one-out sensitivity methods and Egger's test to identify potential studies contributing to the observed heterogeneity (Supplementary Fig. 1). Despite these limitations, they do not undermine the robust conclusions of our article, which assert that HER2 is an emerging biomarker for guiding neoadjuvant treatment in women with early-stage breast cancer.

Conclusion

In conclusion, our meta-analysis supports that HER2-zero status is associated with a significantly higher pathologic complete response (pCR) rate compared to HER2-low status in early-stage breast cancer, but HER2-low status presented longer survival outcomes such as DFS and OS. These findings indicate that HER2-zero status may serve as a relevant prognostic factor in the planning of neoadjuvant treatment for these patients and should be considered during treatment; however, longer follow-up is required for an accurate assessment of these oncological outcomes.

Abbreviations

ADC	Antibody–drug conjugates
BC	Breast cancer
CI	Confidence interval
DCR	Disease control rate
GOSH	Graphical display of study heterogeneity
HR	Hazard ratio
HR+	Hormone receptor positive
I2	I squared statistic (measure of heterogeneity)
IHC	Immunohistochemistry
ISH	In situ hybridization
MeSH	Medical subject headings
NAC	Neoadjuvant chemotherapy
NOS	Newcastle–Ottawa scale
OR	Odds ratio
OS	Overall survival
pCR	Pathological complete response
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
PROSPERO	International prospective register of systematic reviews
RR	Risk ratio
SE	Standart error
SYD985	Trastuzumab duocarmazine
T-DXd	Trastuzumab deruxecan
TNBC	Triple-negative breast cancer
USA	United States of America

Supplementary Information

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Supplementary material 1.

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Author contributions

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Availability of data and materials

All data generated and/or analysed during this study are included in this published article [and its supplementary information files]. Requests for materials should be addressed to F.C.A.M.; francisco.cezar2205@gmail.com.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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