#### **META-ANALYSIS**

# The relationship between tumor budding and survival of patients with breast cancer: A meta-analysis

Hongjie Xu<sup>1</sup> and Dajun Wei<sup>2\*</sup>

Tumor budding has been proposed as a potential prognostic marker in various cancers, but its association with survival outcomes in breast cancer (BC) remains unclear. This meta-analysis aimed to clarify the relationship between tumor budding and survival outcomes in patients with BC. A comprehensive literature search was conducted in PubMed, EMBASE, and Web of Science. Cohort studies examining the association between tumor budding and overall survival (OS) and progression-free survival (PFS) in BC patients were included. Hazard ratios (HRs) and 95% confidence intervals (CIs) were pooled using a random-effects model to account for potential heterogeneity. Eleven cohort studies, including 2828 patients, met the inclusion criteria. High tumor budding was significantly associated with poorer OS (HR = 1.89, 95% CI = 1.37–2.60, P < 0.001) and PFS (HR = 1.89, 95% CI = 1.32–2.71, P < 0.001). Subgroup analyses revealed a stronger association in studies where high tumor budding was defined as  $\geq$  10 buds/high-power field (HPF) compared to those with lower cutoffs. Sensitivity analyses confirmed the robustness of the findings. This meta-analysis demonstrates that high tumor budding is associated with significantly worse OS and PFS in BC patients, underscoring its prognostic significance. These findings suggest tumor budding could be a valuable marker in clinical assessments, and further research is needed to standardize its evaluation criteria in BC.

Keywords: Tumor budding, breast cancer, BC, survival, prognosis, meta-analysis.

#### Introduction

Breast cancer (BC) is the most commonly diagnosed malignancy and a leading cause of cancer-related mortality among women worldwide [1, 2]. Despite advancements in early detection and treatment, BC remains a significant public health burden due to its high prevalence and variability in patient outcomes [3]. Survival rates for BC patients can vary widely based on factors, such as tumor characteristics, treatment modalities, and patient demographics [4–6]. Therefore, identifying reliable prognostic markers and risk factors associated with poor survival is crucial for improving patient management and outcomes. Tumor budding, defined as the presence of isolated single cells or small clusters of up to four cells at the invasive front of tumors [7-9], has emerged as a potential prognostic marker in various cancers, including colorectal [10], pancreatic [11], and esophageal cancers [12]. The mechanisms underlying tumor budding involve epithelial-mesenchymal transition (EMT), where epithelial cells acquire mesenchymal traits, enhancing their migratory and invasive capabilities [13]. This process contributes to tumor progression, metastasis, and resistance to therapy, ultimately leading to a poorer prognosis [14, 15]. In BC, tumor budding is believed to facilitate metastatic spread by enabling cancer cells to dissociate from the primary tumor mass and invade surrounding tissues and distant organs [16]. Evidence has linked tumor budding to several malignant characteristics of BC, such as higher tumor grade, increased lymphovascular invasion, and reduced hormone receptor expression [17, 18].

However, previous studies evaluating the association between tumor budding and BC patient survival have shown inconsistent results [19]. Given the potential of tumor budding as a prognostic marker, this meta-analysis aims to systematically evaluate and quantify the relationship between tumor budding and survival outcomes in BC patients. By synthesizing data from multiple cohort studies, we aim to provide a comprehensive understanding of how tumor budding impacts overall survival (OS) and progression-free survival (PFS) in BC patients. This analysis could inform clinical decision making and guide future research on targeted interventions for patients at higher risk of poor outcomes due to tumor budding.

### **Materials and methods**

This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [20, 21] and the Cochrane Handbook for Systematic

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Reviews and Meta-Analyses [22] throughout its design, data collection, statistical analysis, and interpretation of the results.

#### Data sources and search strategy

A comprehensive literature search was performed in PubMed, EMBASE, and Web of Science to identify relevant cohort studies published from database inception to June 22, 2024. The search strategy included the combined terms of (1) "budding" OR "sprouting" OR "bud" OR "buds" OR "tumor cell dissociation"; (2) "breast cancer"; and (3) "mortality" OR "survival" OR "recurrence" OR "death" OR "prognosis" OR "progression" OR "metastasis." The detailed search strategy for each database is shown in Supplemental File 1. Only studies published in English as full-length articles in peer-reviewed journals were included. Additionally, the reference lists of the identified articles and relevant reviews were screened to ensure comprehensive coverage.

#### Study selection

Studies were included if they met the following criteria designed according to the PICOS model:

- **P** (patients): Patients with a confirmed diagnosis of BC, without limitations on cancer stage or treatment.
- I (exposure): Patients with high tumor budding at enrollment. The methods for evaluating tumor budding and the cutoff values for defining high tumor budding were consistent with those used in the included studies.
- C (comparison): Patients with low tumor budding at enrollment.
- **O** (outcome): Reported at least one of the following outcomes compared between patients with high vs low tumor budding at baseline: OS or PFS. OS was defined as the time from enrollment to death from any cause. PFS was defined as the interval from enrollment to the first BC recurrence or progression.
- **S** (study design): Longitudinal studies, including cohort studies, nested case-control studies, and post hoc analyses of clinical trials.

The exclusion criteria included reviews, editorials, metaanalyses, preclinical studies, cross-sectional studies, studies involving patients with cancers other than BC, and studies that did not report survival outcomes. For studies with overlapping patient populations, the study with the largest sample size was chosen for the meta-analysis.

#### Quality evaluation and data extraction

Two authors independently performed the literature search, study identification, quality evaluation, and data collection. Disagreements were resolved by consensus between the two authors. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) [23], which evaluates studies based on the selection of the study population, comparability between groups, and measurement of exposure. NOS scores ranged from 0 to 9, with higher scores indicating better study quality. A score of 7-9 was considered high quality [23]. Data extracted from each study included study details (authors, year, design, and country), patient characteristics (diagnosis, sample size, age, tumor stage, and main treatments), methods for evaluating tumor budding and cutoffs for defining high tumor budding, follow-up duration, outcomes reported, and variables adjusted for in evaluating the association between tumor budding and survival outcomes of BC patients.

#### Statistical analysis

The association between tumor budding and survival outcomes in BC was summarized using hazard ratios (HRs) and 95% confidence intervals (CIs). HRs and standard errors (SEs) were calculated from 95% CIs or P values, and logarithmic transformation was applied to stabilize and normalize variance. Study heterogeneity was assessed using the Cochrane Q test and  $I^2$  statistics, with  $I^2 > 50\%$  indicating significant statistical heterogeneity [24]. Given the clinical variability among the studies (e.g., patient characteristics, treatments, cutoffs for defining high tumor budding, and follow-up durations), a random-effects model using the inverse-variance approach with DerSimonian and Laird was used for all meta-analyses to account for between-study heterogeneity [22]. Sensitivity analyses were performed by sequentially omitting each study to test the robustness of the results. A predefined subgroup analysis was conducted to evaluate how study characteristics, such as country, cutoff for defining high tumor budding, mean age, follow-up duration, and analytic models (multivariate or univariate analysis), affected the results. Publication bias was initially assessed using funnel plots and visual inspection of symmetry [25], followed by Egger's regression test [25]. Statistical analyses were performed using RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata (version 12.0; Stata Corporation, College Station, TX, USA), with a two-sided *P* value < 0.05 considered statistically significant.

#### Results

#### Database search and study inclusion

The study inclusion process is illustrated in Figure 1. Initially, 564 potentially relevant records were retrieved from the three databases, of which 78 were removed due to duplication. After screening titles and abstracts, 459 studies were further excluded, primarily because they were not relevant to the metaanalysis. Two independent authors reviewed the full texts of the remaining 27 records and excluded 16 additional studies for reasons detailed in Figure 1. Ultimately, 11 cohort studies were deemed suitable for quantitative analysis [26–36].

#### Characteristics of the included studies

Table 1 summarizes the characteristics of the included studies. The meta-analysis included 11 retrospective cohort studies [26–36], conducted in China, the United States, Turkey, Canada, Japan, Portugal, and Iran. One study reported data on different histological types of BC (ER+/HER2- and triple-negative BC [TNBC]), and these datasets were included independently in the meta-analysis [27]. Overall, 2828 patients with BC were included, with mean ages ranging from 52 to 63 years. Eight studies included patients with stage I-III BC [26–31, 33, 34], while two studies included patients with



Figure 1. The flowchart shows database search process and study inclusion. PFS: Progression-free survival; OS: Overall survival.

stage I-IV BC [35, 36]. Surgical resection was the main treatment in ten studies [26-35]. Tumor budding analysis was performed using Hematoxylin and Eosin (H&E) staining in ten studies [26-30, 32-36], while one study used pan-cytokeratin immunohistochemistry [31]. The microscopic magnifications were either  $200 \times [26-34, 36]$  or  $400 \times [35]$ . The cutoff for defining high tumor budding was 5 buds per high-power field (HPF) in seven studies [26-28, 32, 33, 35, 36], 7 buds/HPF in one study [29], 8 buds/HPF in another [31], and 10 buds/HPF in two studies [30, 34]. The median follow-up durations ranged from 7.2-101 months. OS was reported in nine studies [26-30, 32, 34-36], and PFS was reported in eight studies [26, 27, 29-31, 33-35]. Multivariate analyses adjusting for variables such as age, tumor grade, stage, and lymphovascular invasion were performed in six studies [26, 27, 29–31, 34], while univariate analyses were performed in the remaining five studies [28, 32, 33, 35, 36]. The NOS scores of the included studies ranged from six to nine stars, indicating moderate-tohigh study quality (Table 2).

Association between tumor budding and OS of patients with BC Pooled results from ten datasets across nine studies [26-30, 32, 34-36] revealed that high tumor budding at enrollment was associated with poor OS in patients with BC compared to low tumor budding (HR = 1.89, 95% CI = 1.37-2.60, P < 0.001; Figure 2A) with moderate heterogeneity ( $I^2 = 53\%$ ). Sensitivity analysis, where one study was omitted at a time, did not significantly alter the results (HR: 1.53-2.05, all P < 0.05). Subgroup analyses showed similar results in studies from both Asian and Western countries (P for subgroup difference = 0.60; Figure 2B). Interestingly, subgroup analysis suggested a stronger association in studies with a high tumor budding cutoff of  $\geq$  10 buds/HPF (HR = 4.48, 95%) CI = 2.51-7.98), compared to studies using cutoffs of  $\geq$  7 buds/HPF (HR = 3.11, 95% CI = 1.00-9.63) and > 5 buds/HPF (HR = 1.48, 95% CI = 1.20-1.82), which fully explained the heterogeneity (*P* for subgroup difference = 0.001; Figure 2C). Further subgroup analyses based on mean age (P for subgroup difference = 0.10; Figure 3A), follow-up duration (P for

			0,	Sample	Mean age		Main		Microscopic	Cutoff	Median follow-up duration		
Study	Location	Design	Diagnosis	size	(years)	Stage	treatment	Stains	magnification	values	(months)	Outcomes	Variables adjusted
Sun, 2014	China	RC	Operable invasive ductal BC	146	52	≡ _	Surgical resection	H&E	×200	≥5 buds/HPF	46	OS and PFS	Age, tumor stage, grade, LVI, ER/PR expression, and HER-2 expression
Li, 2017 ER+/HER2-	The US	RC	ER+/HER2- BC	244	55.2	=	Surgical resection	H&E	×200	≥5 buds/HPF	72.7	OS and PFS	Age, tumor size, stage, and LVI
Li, 2017 TNBC	The US	RC	TNBC	131	56.2	=	Surgical resection	H&E	×200	≥5 buds/HPF	7.2	OS and PFS	Age, tumor size, stage, and LVI
Okcu, 2021	Turkey	RC	Operable invasive ductal BC	311	57.2	≡ _	Surgical resection	H&E	×200	≥7 buds/HPF (ROC curve analysis derived)	47	OS and PFS	Age, tumor stage, grade, LVI, ER/PR expression, HER-2 expression, and Ki-67 group
Mozarowski, 2021	Canada	RC	Operable BC	75	58.9	≡ _	Neo-adjuvant therapy and surgical resection	H&E	×200	≥5 buds/HPF	50	SO	None
Xiang, 2022	China	RC	Invasive BC	229	NR	≡ _	Surgical resection	Pan- cytokerati IHC	n ×200	≥8 buds/HPF (X-Tile derived)	43.5	PFS	Age, tumor stage, grade, and HER2 expression
Hiratsuka, 2022	Japan	RC	Operable invasive ductal BC	855	56	≡	Surgical resection	H&E	×200	≥10 buds/HPF	58	OS and PFS	Age, tumor stage, grade, LVI, ER/PR expression, HER-2 expression, Ki-67 group, and anticancer treatment
Silva, 2023	Portugal	RC	Early BC	100	63		Lumpectomy or mastectomy	H&E	×200	≥5 buds/HPF	101	PFS	None
Ozer, 2023	Turkey	RC	Invasive BC	198	56.2	NR	Surgical resection	H&E	× 200	≥5 buds/HPF	39.6	SO	None
Hou, 2024	China	RC	TNBC	118	NR	-	Surgical resection	H&E	× 200	≥10 buds/HPF	40	OS and PFS	Age, tumor size, grade, stage, and Ki-67 groups
Ranaee, 2024	Iran	RC	Invasive BC	150	54	VI-I	NR	H&E	×200	≥5 buds/HPF	30	SO	None
Ozsen, 2024	Turkey	RC	Invasive BC	271	54.8	<u>&gt; − </u>	Surgical resection	H&E	×400	≥5 buds/HPF	60	OS and PFS	None
BC: Breast canc OS: Overall sur	cer; ER: Estrc vival; PFS: Pı	ogen recel rogression	ptor; HER-2: Human e n-free survival; PR: Pr	piderma ogestero	l growth ne rece	ו factor רפ ptor; RC:	:ceptor 2; H&E: Hema Retrospective cohort	atoxylin ano ; ROC: Rece	d Eosin; HPF: Hi; eiver operating (	gh-power field; IHC characteristic; TNB	: Immunoh C: Triple-n	iistochemistry; egative breast	LVI: Lymphovascular invasion; cancer; NR: Not reported.

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#### Table 2. Study quality evaluation via NOS

Study	Representa -tiveness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Sun, 2014	0	1	1	1	1	1	1	1	1	8
Li, 2017 ER+/HER2-	0	1	1	1	1	1	1	1	1	8
Li, 2017 TNBC	0	1	1	1	1	1	1	0	1	7
Okcu, 2021	0	1	1	1	1	1	1	1	1	8
Mozarowski, 2021	0	1	1	1	0	0	1	1	1	6
Xiang, 2022	0	1	1	1	1	1	1	1	1	8
Hiratsuka, 2022	1	1	1	1	1	1	1	1	1	9
Silva, 2023	0	1	1	1	0	0	1	1	1	6
Ozer, 2023	0	1	1	1	0	0	1	1	1	6
Hou, 2024	0	1	1	1	1	1	1	1	1	8
Ranaee, 2024	0	1	1	1	0	0	1	1	1	6
Ozsen, 2024	0	1	1	1	0	0	1	1	1	6

NOS: Newcastle-Ottawa scale.

subgroup difference = 0.52; Figure 3B), and analytic models (P for subgroup difference = 0.16; Figure 3C) yielded similar results.

# Association between tumor budding and PFS of patients with BC

The meta-analysis of nine datasets from eight studies [26, 27, 29–31, 33–35] indicated that patients with high tumor budding had significantly poorer PFS compared to those with low tumor budding (HR = 1.89, 95% CI = 1.32–2.71, P < 0.001; Figure 4A). Sensitivity analysis, excluding one dataset at a time, produced similar results (HR: 1.58–2.10, P < 0.05).

Subgroup analysis revealed a stronger association between high tumor budding and poor PFS in studies conducted in Asian countries compared to non-Asian countries (HR: 2.77 vs 1.28, *P* for subgroup difference = 0.01; Figure 4B), though significant heterogeneity was noted among Asian studies ( $I^2 = 71\%$ ). Additionally, subgroup analysis based on tumor budding cutoffs demonstrated a stronger association in studies using a cutoff of > 10 buds/HPF (HR = 5.21, 95% CI = 3.01-9.01) compared to cutoffs of > 7 or 8 buds/HPF (HR = 1.94, 95% CI = 1.32–2.84) and > 5 buds/HPF (HR = 1.34, 95% CI = 1.05-1.70), fully explaining the heterogeneity (*P* for subgroup difference < 0.001; Figure 4C). Further subgroup analyses based on mean age (P for subgroup difference = 0.56; Figure 5A), follow-up duration (P for subgroup difference = 0.66; Figure 5B), and analytic models (*P* for subgroup difference = 0.35; Figure 5C) showed consistent results.

#### **Publication bias**

Funnel plots for the associations between tumor budding and OS and PFS in BC patients appeared symmetrical, suggesting minimal publication bias (Figure 6A and 6B). Egger's tests further confirmed low publication bias for OS and PFS (P = 0.52 and 0.66, respectively).

#### Discussion

This meta-analysis aimed to clarify the relationship between tumor budding and survival outcomes in BC patients. The findings revealed a significant association between high tumor budding and poorer OS and PFS. Specifically, patients with high tumor budding had an approximately 89% increased risk of mortality and a similar increase in the risk of disease progression compared to those with low tumor budding. These results highlight the prognostic value of tumor budding in BC and suggest that it could serve as an important marker for identifying patients at higher risk of adverse outcomes. Several potential mechanisms might explain the link between high tumor budding and poor survival in BC. Tumor budding is closely related to epithelial-mesenchymal transition (EMT), a process in which epithelial cells lose their cell-cell adhesion properties and gain migratory and invasive capabilities [37]. EMT is driven by several molecular pathways, including the activation of transcription factors, such as Snail, Slug, and Twist, which repress E-cadherin expression and promote the expression of mesenchymal markers like N-cadherin and vimentin [38]. Additionally, signaling pathways involving TGF- $\beta$ , Wnt/ $\beta$ -catenin,

Bit duy or Subgroup         log(Hazard Ratio)         EW wight         IV. Random. 95% CI         N. Random. 95% CI           Sur 2014         0.4167347         0.2717         10.2%         1.52 (0.73, 3.14)           Li 2017 TNNE         0.4167347         0.2717         10.2%         1.53 (0.65, 4.38)           Li 2017 TNNE         0.4167347         0.2717         10.2%         1.52 (0.73, 3.14)           Mazarowski 2021         1.1346227         0.57653         5.5%         3.111 (1.00, 9.63)           Mazarowski 2021         1.1346277         0.30644         2.3%         4.55 (2.46, 8.29)           Hatsuka 2022         1.03032822         1.070449         2.3%         4.55 (2.46, 8.29)           Ramez 2024         0.22314350         0.17377         10.2%         1.81 (1.72, 8.170)           Ozen 2024         0.227002714         0.310686         9.9%         1.31 (0.82, 1.70)           Mearoogeneky Taw're 0.12%         S.E. Weight I. V. Random. 95% CI         Hazard Ratio         Hazard Ratio           Sub 2016         0.66752         0.27677         10.2%         1.52 (0.73, 3.14)           Hiercogeneky Taw're 0.40; CP = 1.40, 4, dr = 2 (P = 0.00;); P = 79%         11.31 (5.26, 9.176)         Hazard Ratio           Li 2017 ER-HER2.         0.65752         0.416277<	A					Hazard Ratio		Hazard Ratio	
	_	Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
Li 2017 FR-HER2. 0.8572 0.418257 8.9% 1.93 (0.85, 4.38) Li 2017 TNEC 0.450756 0.20057 15.9% 15.71 (0.4, 2.37) Okcu 2021 1.1346227 0.5763 5.9% 3.111 (0.0, 9.63) Mazarowski 2021 0.11332680 0.4602 8.3% 1.12 (0.4, 7.26) Hintsuka 2022 1.0303282 1.073048 2.1% 3.70 (0.4, 5.03) Hazard Ratio Phetrogeneity: Taw = 0.12; Chir = 19.0, df = 9 ( $P = 0.02$ ); P = 53% Tast for overall effect: Z = 3.88 ( $P = 0.0001$ ) B <u>Study or Subgroup logithazard Ratio</u> JSE Weight IV AS 1.125 (0.73, 176) Hazard Ratio Hazard Ratio Hazar		Sun 2014	0.4167347	0.371787	10.2%	1.52 [0.73, 3.14]		+	
Li 2017 TNEC 0.45107582 0.208975 15.9% 1.57 (1.0.4.2.37) Mazarowski 2021 0.11332689 0.445042 8.3% 1.12 (0.47, 2.68) Mazarowski 2021 0.11332689 0.445042 8.3% 1.12 (0.47, 2.68) Mazarowski 2021 1.0144767 0.30858 2.1% 3.70 (0.45, 3.03) Hazard Ratio Heterogeneity: Tar = 0.12 C.DH = 18, 10, df = 9 (P = 0.02); P = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Heterogeneity: Tar = 0.12 C.DH = 18, 10, df = 9 (P = 0.02); P = 53% Li 2017 NEC 0.451753 0.173841 17.4% 1.25 (0.86, 1.76) Mazard Ratio Heterogeneity: Tar = 0.12 C.DH = 18, 10, df = 9 (P = 0.02); P = 53% Li 2014 0.4167347 0.371787 10.2% 1.52 (0.73, 3.14] Hintsuka 2022 1.3083282 1.073048 2.1% 3.70 (0.45, 30.31] Hou 2024 0.22014 0.217464707 0.371787 10.2% 1.52 (0.73, 3.14] Hintsuka 2022 1.3083282 1.073048 2.1% 3.70 (0.45, 30.31] Hou 2024 1.51446707 0.371787 10.2% 1.52 (0.73, 3.14] Hintsuka 2022 1.021446707 0.371787 10.2% 1.52 (0.73, 3.14] Hintsuka 2022 1.0343282 1.073048 2.1% 3.70 (0.45, 30.31] Hou 2024 1.51446707 0.371787 10.2% 1.52 (0.73, 3.14] Hintsuka 2022 1.01436273 0.67653 5.9% 3.11 (1.00, 9.63] Mazard Ratio Mazard Ratio Mazard Ratio Hintsuka 2022 1.01446727 0.37765 5.9% 5.157 (1.04, 2.37] Namea 2024 0.27002714 0.381589 9.9% 1.33 (0.65, 4.38] Li 2017 FNEC 0.46107562 0.208675 1.59% 1.57 (1.04, 2.37] Mazard Ratio Mazard Ratio Ma		Li 2017 ER+/HER2-	0.65752	0.418257	8.9%	1.93 [0.85, 4.38]			
$ \begin{array}{c} \text{Obc} 2021 & 1.13462273 0.5763 5.5\% 1.511(10,0,9.63] \\ \text{Mazarowski 2021} & 1.1346227 0.57653 5.5\% 1.511(1,12,0.47,2.66] \\ \text{Hatasuka 2022} & 1.0303282 1.073048 2.1\% 3.70[0.45, 30.31] \\ \text{Ozer 2023} & 1.1682769 0.410627 9.1\% 3.251(1.43,7,16] \\ \text{Hatasuka 2024} & 1.5446777 0.306644 12.3\% 4.55[2.48, 8.29] \\ \text{Hatasuka 2024} & 0.227032714 0.351658 9.9\% 1.310[0.5, 2.77] \\ \text{Total (95% C)} & 0.27002714 0.351658 9.9\% 1.310[0.5, 2.77] \\ \text{Total (95% C)} & 0.27002714 0.351659 9.9\% 1.310[0.5, 2.77] \\ \text{Total (95% C)} & 0.27102714 0.35165 9.9\% 1.38 [1.37, 2.60] \\ \text{Heterogenetity: Tau' = 0.12; Chi2 = 19, 0.0 d1 = 9 (P = 0.02); P = 53% \\ \text{Total countries} & 1.21 Asin countries \\ \text{Sun 2014} & 0.4167347 0.371787 10.2\% 1.52 [0.7, 3.14] \\ \text{Hintsuka 2022} & 1.03032282 10.73048 2.1\% 3.70 [0.45, 3.31] \\ \text{Heterogenetity: Tau' = 0.4; Chi2 = 1.40, dt = 3 (P = 0.02); P = 53\% \\ \text{Test for overall effect: Z = 1.38 (P = 0.05) \\ \textbf{1.22 Western countries} \\ \textbf{1.2 Other countries} & 1.30 (0.2, 2.33455 0.17341 17.4\% 1.52 [0.73, 3.14] \\ \text{Heterogenetity: Tau' = 0.4; Chi2 = 1.40, dt = 3 (P = 0.03); P = 75\% \\ \text{Test for overall effect: Z = 1.38 (P = 0.05) \\ \textbf{1.2 Western countries} \\ \textbf{1.2 Other countries} & 1.23 (0.85, 1.76] \\ \textbf{1.2 Western countries} \\ \textbf{1.2 Other Environes} & Chi2 = 0.003; P = 75\% \\ \text{Test for overall effect: Z = 1.38 (P = 0.001) \\ \textbf{1.2 Other Subcroup} & 0.65752 0.418257 8.9\% 1.193 [0.85, 4.38] \\ \textbf{1.2 Other Subcroup} & 0.65752 0.418257 8.9\% 1.131 [0.6, 2.37] \\ \text{Mozarowski 2021} & 0.1182278 0.47663 5.5\% 1.571 [1.40, 2.37] \\ \text{Mozarowski 2021} & 0.1182278 0.4763 5.5\% 1.571 [1.40, 2.37] \\ \text{Mozarowski 2021} & 0.1182278 0.47663 5.5\% \\ \text{Subtoal} (9\% C) & 0.0072797177 10.2\% \\ \text{Subtoal} (9\% C) & 0.0074797177 10.2\% \\ \text{Subtoal} (9\% C) & 0.0074797177 10.2\% \\ Metorogenetic; Tau' = 0.2; Chi2 = 5.0\% \\ \text{Test for overall effect: Z = 3.86 (P = 0.0001) \\ \text{Test for overall effect: Z = 3.86 (P = 0.0001) \\ \text{Test for overall effect: Z = 3.86 (P = 0.0001) \\ \text{Test for overall effect: Z = 3.86 (P = 0.0001) \\ \text{T$		Li 2017 TNBC	0.45107562	0.209875	15.9%	1.57 [1.04, 2.37]			
$ \begin{array}{llllllllllllllllllllllllllllllllllll$		Okcu 2021	1.13462273	0.57653	5.9%	3.11 [1.00, 9.63]			
$ \begin{array}{c} \mbox{Prince} \label{eq:prince} \mbox{Prince} \mbo$		Mozarowski 2021	0.11332869	0.445042	8.3%	1.12 [0.47, 2.68]			
$ \begin{array}{c} \text{C} \begin{array}{c} \text{C} \\ \text{Paranee 2024} \\ \text{Paranee 2024} \\ \text{C2281 022 Miss 0.1739H 117.74\% 125 (0.89, 1.76)} \\ \text{C2281 0227 M02714 0.31658 9.95\% 1.31 (0.62, 2.71)} \\ \text{Treat or overall effect: 2 = 3.88 (P = 0.001) \\ \text{Heterogeneity: Tau" = 0.12; Chi" = 19.10, df = 9 (P = 0.02); P = 5.35\% \\ \text{Treat or overall effect: 2 = 3.88 (P = 0.001) \\ \text{Study or Subgroup log(Hazard Ratio } \\ Study or Subgroup log(Chi" = 5.06, df = 5.06, ff = 0.02); P = 53\% \\ \text{Test for overall effect: 2 = 3.78 (P = 0.002); P = 53\% \\ \text{Test for overall effect: 2 = 3.78 (P = 0.002); P = 53\% \\ \text{Test for overall effect: 2 = 3.78 (P = 0.002); P = 53\% \\ \text{Test for overall effect: 2 = 3.78 (P = 0.002); P = 53\% \\ \text{Test for overall effect: 2 = 3.78 (P = 0.002); P = 53\% \\ \text{Test for overall effect: 2 = 3.78 (P = 0.002); P = 53\% \\ \text{Test for overall effect: 2 = 3.78 (P = 0.002); P = 53\% \\ \text{Test for overall effect: 2 = 3.78 (P = 0.002); P = 53\% \\ \text{Test for overall effect: 2 = 3.78 (P = 0.002); P = 53\% \\ \text{Test for overall effect: 2 = 3.80$		Hiratsuka 2022	1.30833282	1.073048	2.1%	3.70 [0.45, 30.31]			
$ \begin{array}{c} \begin{array}{c} 1.22344356 0.723441 17.44\% 1.25 (0.83, 1.26) \\ \hline 1.22344356 0.723441 17.44\% 1.25 (0.83, 1.26) \\ \hline 1.22344356 0.72344 0.23704271 0.331658 9.9\% 1.31 (0.62, 2.77) \\ \hline 1.24 (0.65, 0.2) \\ \hline 1.25 (0.65, 0.2) \\ \hline 1.24 (0.65, 0.2) \\ \hline 1.24 (0.65, 0.2) \\ \hline 1.25 (0.65, 0.2) \\ \hline 1.25 (0.65, 0.2) \\ \hline $		Ozer 2023	1.1002/094	0.410927	9.1%	3.21 [1.43, 7.16]			
Ozsen 2024       0.27002714       0.381858       9.9%       1.31       0.62. 2.77         Total (95% C)       100.0%       1.89 [1.37, 2.60]       100.0%       1.89 [1.37, 2.60]         B       Study or Subgroup       log(Hazard Ratio       Hazard Ratio       Hazard Ratio         Sun 2014       0.4167347       0.371787       10.2%       1.52 [0.73, 3.14]         Hatzard Ratio       Hazard Ratio       Hazard Ratio       Hazard Ratio         Sun 2014       0.4167347       0.371787       10.2%       1.52 [0.73, 3.14]         Hetrogeneity: Tau" = 0.40; Chi" = 1.40, df = 3 (P = 0.003); I" = 79%       Total (9% C)       Hazard Ratio       Hazard Ratio         Subtotal (9% C)       0.4167247       0.371637       1.52 [0.73, 3.14]       Hazard Ratio       Hazard Ratio         Li 2017 ER-HER2       0.45107862       0.419827       8.9%       1.33 [0.85, 4.38]       1.12 [0.47, 2.80]         Li 2017 TR-HER2       0.45107862       0.419827       8.9%       1.31 [0.02, 2.71]       1.57 [1.04, 2.37]         Occur 2021       1.132260       Add (H = 3 (P = 0.002); P = 0.33); H = 7.78;       1.10 (0.2, 6.3]       1.11 [0.0, 6.8]         Mozarowski 2021       0.1332680       4.40422       3.8, 1%;       1.72 [1.30, 2.29]       Hetrogeneity: Tau" = 0.20; Chi" = 5.06;		Ranaee 2024	0 22314355	0.300044	17.4%	4.55 [2.49, 0.29]			
Total (6% C) 100.0% (1.88 [1.37, 2.60] Heterogenety: Tat <sup>2</sup> = 0.12; Ch <sup>2</sup> = 19.10, df = 9 (P = 0.02); P = 53% Test for overall effect: Z = 3.88 (P = 0.001) B <u>Study or Subgroup log(Hazard Ratio</u> SE Weight IV. Random, 95%; Cl IV. Random, 95%;		Ozsen 2024	0.27002714	0.381858	9.9%	1.31 [0.62, 2.77]		<b>—</b>	
Total (95% CI) 100.0% 1.89 [1.37, 2.60] Heterogenetic; Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.00, 19 = 0.02; P = 53% Test for overall effect: 2 = 3.88 (P = 0.0001) Hazard Ratio 1.2.1 Asian countries Sun 2014 0.4167347 0.371787 10.2% 1.52 [0.73, 3.14] Hinasuka 2022 1.30833282 1073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% Sub 2014 0.421734355 0.173941 17.4% 1.25 [0.89, 1.76] Sub 2014 0.56752 0.418257 8.9% 1.33 [0.85, 4.38] Li 2017 EN+/HER2- 0.65752 0.418257 8.9% 1.33 [0.85, 4.38] Li 2017 TNBC 0.45107562 0.209675 f.59% 1.37 [10.4, 2.37] Okcu 2021 1.13426273 0.57653 5.9% 3.11 [1.00, 9.63] Mozarowall effect: Z = 1.38 (P = 0.002) Total (95% CI) 1.132266 0.4410927 9.1% 3.21 [1.43, 7.18] Ozera 2023 1.16827094 0.410927 9.1% 3.21 [1.43, 7.18] Ozera 2024 0.22704124 0.31858 9.9% 1.31 [0.62, 2.77] Sub total (95% CI) 1.00 Chi <sup>2</sup> = 5.08, df = 5 (P = 0.041); P = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.88 (P = 0.0001) Test for subaround inferences: Chi <sup>2</sup> = 0.28, df = 1 (P = 0.06); P = 0% C Subdaving Ci, Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.08, df = 5 (P = 0.02); P = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for subaround inferences: Chi <sup>2</sup> = 0.28, df = 1 (P = 0.06); P = 0% C Subdaving Ci 1.132 266 0.445042 8.38; 1.12 [0.47, 2.68] Ozer 2023 1.16827094 0.416927 9.1% 3.21 [1.43, 7.18] Ozer 2023 1.16827094 0.416927 9.1% 1.32 [0.73, 3.14] Li 2017 TNBC 0.45107562 0.209875 15.9% 1.37 [1.04, 2.37] Mozarowall 2021 0.00; Chi <sup>2</sup> = 5.08, df = 0.00; P = 0.00; P = 0.00; Test for overall effect: Z = 3.82 (P = 0.000) Test for overall effect: Z = 3.82 (P = 0.000) Test for overall effect: Z = 3.82 (P = 0.000) Test for overall effect: Z = 3.82 (P = 0.000) Test for overall effect: Z = 1.97 (P = 0.05) 1.3.3 ≥ 10 buddHPF Harsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 3.0.31] Heterogeneity: Tau <sup>2</sup>									
Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 13.0; df = 9 (P = 0.02); P = 53% Test for overall effect: Z = 3.88 (P = 0.0001) <b>B</b> Study or Stubgroup togHazard Ratio 1.2.1 Asian countries Sun 2014 0.4167347 0.371787 10.2% 1.52 (D.73, 3.14) Hratsuka 2022 1.3085322 1.073048 2.1% Subtotal (95% Cl) 4.15446767 0.306644 12.3% 4.55 [2.49, 8.29] Ranee 2024 0.2214355 0.173941 17.4% 1.25 [0.89, 1.76] Subtotal (95% Cl) 4.15446767 0.30763 5.9% 1.93 [0.85, 4.38] Li 2017 TNBC 0.45107562 0.209875 15.9% 1.57 [1.04, 2.37] Mozarowski 2021 0.1132869 0.445042 8.3% 1.12 [0.47, 2.68] Mozarowski 2021 0.1132869 0.45502 9.55% 3.111 [1.00, 9.63] Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> = 0.28, df = 1 (P = 0.02); F = 53% Test for overall effect: Z = 3.82 (P = 0.0001) Tast for subdriveF Mozarowski 2021 0.1132869 0.45502 9.55% 3.111 [1.00, 9.63] Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> = 0.47; J = 0.0; Task 3.74, df = 6 (P = 0.48); F = 0% Test for overall effect: Z = 3.82 (P = 0.0001) Tast for overall effect: Z = 3.88 (P = 0.0001) Tast for overall effect		Total (95% CI)			100.0%	1.89 [1.37, 2.60]		•	
Test for overall effect: $Z = 3.88$ (P = 0.0001) Hazard Ratio Study or Subgroup togHazard Ratio SE Weight IV. Random. 95% CI 1.2.1 Asian countries Sun 2014 Hiratsuka 2022 1.3083282 1073048 Sun 2014 Hiratsuka 2022 1.3083282 1073048 2.1% 3.70 [0.45, 90.31] How 2024 1.51 6446767 0.306644 1.2.3% Subtotal (65% CI) 1.2.2 Western countries Li 2017 ER-HER2- 0.65752 0.418257 0.65752 0.418257 0.65752 0.418257 1.59% 1.57 [1.04, 2.37] Okcu 2021 1.1342627 0.56752 0.418257 0.65752 0.418257 0.65752 0.418257 0.65752 0.418257 0.65752 0.418257 0.5815% 1.17 [1.04, 2.37] Okcu 2021 1.138268 0.20875 1.59% 1.37 [1.04, 2.37] Okcu 2024 1.19827094 0.419927 Subtotal (65% CI) 1.2.2 Western countries Li 2017 ER-HER2- 0.05752 0.418257 0.65752 0.418257 0.657 0.00 Chi <sup>2</sup> = 5.06, df = 5 (P = 0.41); F = 1% Test for overall effect: Z = 3.88 (P = 0.0001) Test for subdroup log[Hazard Ratio V. Random. 95% CI V. Random. 95% CI V. Random. 95% CI V. Random. 95% CI V. Random. 95% CI 1.3.1 $\geq$ 5 budsMHPF Sun 2014 U2017 TR-HER2- 0.65752 0.418257 0.5753 0.59% 3.111 [1.00, 9.63] Heterogenetiy: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 (P = 0.48); F = 0% Test for overall effect: Z = 3.82 (P = 0.003) 1.3.2 $\geq$ 7 buds/HPF Hiratsuka 2022 1.3.82 $\geq$ 7 buds/HPF Hiratsuka 2022 1.3.82 $\geq$ 7 buds/HPF Hiratsuka 2022 1.3.83282 1.073048 2.1% 3.111 [1.00, 9.63] Heterogenetiy: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 (P = 0.48); F = 0% Test for overall effect: Z = 1.387 (P = 0.05) 1.3.2 $\geq$ 7 buds/HPF Hiratsuka 2022 1.3.83282 1.073048 2.1% 3.70 [0.45, 3.031] Heterogenetiy: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.05) 1.3.2 $\geq$ 7 buds/HPF Hiratsuka 2022 1.3.83282 1.073048 2.1% 3.70 [0.45, 3.031] Heterogenetiy: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03; F = 0.03; F =		Heterogeneity: Tau <sup>2</sup> =	0.12; Chi² = 19.10, df	= 9 (P = 0.	.02); I <sup>2</sup> = 5	3%	0.05	02 1 5	20
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		Test for overall effect: 2	Z = 3.88 (P = 0.0001)	)			0.00		
B         Study or Subgroup         Leg(Hazerd Ratio)         SE         Weight         IV. Random. 95% Cl         IV. Random. 95% Cl           1.2.1 Asian countries         1.3.083282         1.073048         2.1%         3.70 [0.45, 30.31]           1.0.1 Asian countries         1.3.083282         1.073048         2.1%         3.70 [0.45, 30.31]           1.0.1 Asian countries         1.3.1644676         0.030644         1.2.3%         4.55 [2.4, 8.22]           Ranace 2024         0.22314355         0.173941         1.7.4%         1.25 [0.59, 1.76]           1.2.2 Western countries         1.2017 ER-/HER2-         0.65752         0.418257         8.9%         1.33 [0.85, 4.38]           1.2.1 VBC         0.45107562         0.209675         1.59%         1.37 [1.04, 2.37]           Occu 2021         1.132668         0.456024         8.3%         1.12 [0.47, 2.68]           Ozera 2023         1.16827094         0.419827         9.58.1%         1.32 [1.32, 2.60]           Heterogeneity: Tau' = 0.01; Chi" = 1.0. df = 9 (P = 0.02); P = 53%         1.37 [1.02, 2.27]         0.005         0.2         1         5           1.2.1 VBC         0.4167347         0.371787         10.2%         1.52 [0.73, 3.14]         1.42 [1.42, 4.237]           Total (95% Cl)         0.27	D					Hazard Ratio		Hazard Ratio	
<b>1.2.1</b> Asian countries Sun 2014 0.4167347 0.371787 10.2% 1.52 [0.73, 3.14] Hiratsuka 2022 1.30383282 1.073048 2.1% 3.70 [0.45, 30.31] How 2024 1.51446767 0.306644 12.3% 4.56 [2.48, 8.29] Rannee 2024 0.22314355 0.173841 17.4% 1.25 [0.89, 1.76] Subtoal (9% C) <b>1.2.2</b> Western countries L12017 TR4C 0.46107562 0.418257 8.9% 1.93 [0.85, 4.38] L12017 TR4C 0.45107562 0.208975 15.9% 3.11[10.0, 9.63] Mozarowski 2021 0.11332689 0.445042 8.3% 1.12 [0.47, 2.68] Mozarowski 2021 0.11332689 0.445042 8.3% 1.12 [0.47, 2.68] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5.66, df = 5 (P = 0.02); P = 53% Test for overall effect: Z = 3.78 (P = 0.0001) Test for suborou differences: Ch <sup>2</sup> = 0.28, df = 1 (P = 0.60, P = 0% <b>C</b> <b>Study or Suborou differences:</b> Ch <sup>2</sup> = 0.28, df = 1 (P = 0.02); P = 53% L12107 TR8C 0.45107542 0.208975 10.2% 1.52 [0.73, 3.14] L12017 TR4C 0.45107562 0.418257 8.9% 1.31 [0.62, 2.77] Subtoal (95% C) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.10; Ch <sup>2</sup> = 15.06, df = 5 (P = 0.02); P = 53% Test for overall effect: Z = 3.78 (P = 0.0002) <b>Total (95% C)</b> 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.02; Ch <sup>2</sup> = 19.10, df = 9 (P = 0.02); P = 53% Subtoal (Bferences: Ch <sup>2</sup> = 0.28, df = 1 (P = 0.60), P = 0% <b>C</b> <b>Study or Subgroup log(Hazard Ratio) SE Wield IV. Random, 95% CI</b> <b>1.31</b> ≥ 5 buds/HPF Sun 2014 0.4167347 0.371787 10.2% 1.52 [0.73, 3.14] L12017 TR4/HER2 0.65752 0.418257 8.9% 1.31 [0.62, 2.77] Mozarowski 2021 0.11332869 0.445042 8.3% 3.11 [10.0, 9.63] Mozarowski 2021 0.11332869 0.445042 8.3% 3.11 [10.0, 9.63] Subtoal (95% C) 73.44 17.4% 1.25 [0.80, 1.76] <b>Total (95% C)</b> 1.13462273 0.57653 5.9% 3.111 [1.00, 9.63] Subtoal (95% C) 73.43 17.43 (F = 0.003) <b>1.32</b> ≥ 7 buds/HPF Miratsuka 2022 1.2083282 1.073048 2.1% 3.70 [0.45, 30.31] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.00; 17.83 (F = 0.00	Р.	Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
Sun 2014 0.4167347 0.371787 10.2% 1.52 [0.73, 3.14] Hintstuka 2022 1.03083282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Ransee 2024 0.22314355 0.173941 17.4% 1.25 [0.89, 1.76] Subtotal (95% C) 1.2.2 Western countries Li 2017 ER+/HER2 0.65752 0.418257 8.9% 1.93 [0.85, 4.38] Li 2017 TNBC 0.65752 0.418257 8.9% 1.57 [1.04, 2.37] Okcu 2021 1.13462273 0.57653 5.9% 3.111 [1.00, 9.63] Mozarowski 2021 0.011332689 0.445042 8.3% 1.12 [0.47, 2.68] Ozer 2023 1.16827094 0.410927 9.1% 3.21 [1.43, 7.18] Test for overall effect: Z = 3.78 (P = 0.0001) Total (95% C) Heterogeneity: Tau* = 0.00; Chi* = 5.0, di = 5 (P = 0.41); P = 1% Test for overall effect: Z = 3.88 (P = 0.0001) Tast for subbroup log[Hazard Ratio] SE Weight IV. Random, 95% Cl 1.31 $\approx$ 5 budsHPF Sun 2014 0.4167347 0.371787 10.2% 1.52 [0.73, 3.14] Li 2017 TR+/HER2 0.65752 0.418257 8.9% 1.31 [1.00, 9.63] Subtotal (95% C) Total (95% C) Tast for overall effect: Z = 3.88 (P = 0.0001) Tast for subbroup log[Hazard Ratio] SE Weight IV. Random, 95% Cl 1.31 $\approx$ 5 budsHPF Sun 2014 0.4167347 0.371787 10.2% 1.52 [0.73, 3.14] Li 2017 TR+/HER2 0.65752 0.418257 8.9% 1.37 [1.02, 4.37, 18] Ransee 2024 0.22314355 0.173941 17.4% 1.25 [0.89, 1.76] Ozera 2023 1.16827094 0.419927 9.1% 3.21 [1.43, 7.18] Ransee 2024 0.22314355 0.173941 17.4% 1.25 [0.89, 1.76] Ozera 2023 1.1682704 0.41997 9.9% 1.31 [1.00, 9.63] Subtotal (95% C) 1.32 $\geq$ 7 budsHPF Hintsuka 2022 1.3083282 1.073048 2.1% 3.70 [0.45, 3.031] Heterogeneity: Tau* = 0.00; Chi* = 5.40, dt = (P = 0.48); P = 0% Test for overall effect: Z = 1.97 (P = 0.05) 1.32 $\geq$ 7 budsHPF Hintsuka 2022 1.3083282 1.073048 2.1% 3.70 [0.45, 30.31] Heterogeneity: Tau* = 0.00; Chi* = 5.40, dt = (P = 0.02); P = 63% Test for overall effect: Z = 1.97 (P = 0.05) 1.33 $\geq$ 10 buds/HPF Hintsuka 2022 1.3083282 1.073048 2.1% 3.70 [0.45, 30.31] Heterogeneity: Tau* = 0.00; Chi* = 5.00 (D = 0.48); P = 0% Test for overall effect: Z = 1.97 (P = 0.05); P = 53% Test for overall effect:		1.2.1 Asian countries							
Hintsuka 2022 1.3033282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.48, 8.29] Ranace 2024 0.22314355 0.173941 17.4% 1.25 [0.89, 1.76] Subtoal (95% C) 41.3% 2.14 [1.01, 4.52] Heterogeneity: Tau" = 0.40: Chi" = 14.04, df = 3 (P = 0.003); P = 79% Test for overall effect: Z = 1.98 (P = 0.05) 1.22 Western countries Li 2017 TNBC 0.45107662 0.200975 15.9% 1.57 [1.04, 2.37] Okcu 2021 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Mozarowski 2021 0.11332869 0.445042 8.3% 1.12 [0.47, 2.68] Oczer 2023 1.1662704 0.410927 9.1% 3.21 [1.43, 7.18] Oczer 2024 0.27002714 0.381858 9.9% 1.31 [0.62, 2.77] Subtoal (95% C) 40.10927 9.1% 3.21 [1.43, 7.18] Oczer 2023 1.1662704 0.410927 9.1% 3.21 [1.43, 7.18] Oczer 2023 1.16162704 0.410927 9.1% 3.21 [1.43, 7.18] Oczer 2023 1.16162704 0.410927 9.1% 3.21 [1.43, 7.18] Oczer 2023 1.16162704 0.410927 9.1% 3.21 [1.43, 7.18] Oczer 2023 1.16167347 0.371767 10.2% 1.59 [0.73, 3.14] Li 2017 TNBC 0.45107562 0.200875 15.9% 1.37 [0.58, 4.38] Li 2017 ER-/nHER2- 0.65752 0.2418257 8.9% 1.39 [0.58, 4.38] Li 2017 ER-/nHER2- 0.65752 0.2418257 8.9% 1.39 [0.58, 4.38] Li 2017 ER-/nHER2- 0.65752 0.2418257 8.9% 1.37 [1.04, 2.37] Mozarowski 2021 0.11332869 0.2418257 8.9% 1.39 [0.58, 4.38] Li 2017 TNBC 0.45107562 0.200875 15.9% 1.37 [1.04, 2.37] Mozarowski 2021 0.11332869 0.445042 8.3% 1.12 [0.47, 2.68] Oczer 2023 1.16827064 0.410279 9.1% 3.21 [1.43, 7.18] Ramaee 2024 0.2270174 0.381858 9.9% 1.31 [0.62, 2.77] Subtotal (95% C) 1.13462773 0.57653 5.9% 3.111 [1.00, 9.63] Subtotal (95% C) 1.13462773 0.57653 5.9% 3.111 [1.00, 9.63] Subtotal (95% C) 1.13462773 0.57653 5.9% 3.111 [1.00, 9.63] Subtotal (95% C) 1.144767 0.300644 12.3% 4.55 [2.49, 8.29] Subtotal (95% C) 1.151446767 0.300644 12.3% 4.55 [2.49, 8.29] Subtotal (95% C) 1.151446767 0.300644 12.3% 4.55 [2.49, 8.29] Subtotal (95% C) 1.151446767 0.300644 12.3% 4.55 [2.49, 8.29] Subtotal (95% C) 1.14474 6.9 (P = 0.00;) P = 85.3% Test for overall effect; Z = 3.80 (P = 0.0001) Total (95% C) 1.1642 (P = 0.		Sun 2014	0.4167347	0.371787	10.2%	1.52 [0.73, 3.14]			
Hou 2024 1.51446767 0.30664 12.3% 4.55 [2.49, 8.29] Ranaee 2024 0.22314355 0.773941 17.4% 1.25 [0.89, 1.76] Subtotal (95%, CI) 4.04; Chi <sup>2</sup> = 1.40, df = 3 (P = 0.003); I <sup>2</sup> = 79% Test for overall effect: Z = 1.98 (P = 0.05) 1.22 Western countries Li 2017 TNBC 0.465107562 0.418257 8.5% 1.57 [1.04, 2.37] Okcu 2021 1.13462273 0.57653 5.5% 1.57 [1.04, 2.37] Okcu 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Ozera 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Test for overall effect: Z = 3.88 (P = 0.0001) Total (95% CI) 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.62); I <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.82 (P = 0.0001) Total (95% CI) 0.11332669 0.445042 8.3% 1.12 [0.73, 3.14] Li 2017 TNBC 0.45107562 0.208875 15.9% 1.57 [1.04, 2.37] Metrogenetic; Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.28, df = 1 (P = 0.60), I <sup>2</sup> = 0% C C C C S total (95% CI) 1.00, df = 9 (P = 0.22); I <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for subbroup logHazard Ratio] SE Weight IV. Random, 95% CI V. Random, 95%; CI V.		Hiratsuka 2022	1.30833282	1.073048	2.1%	3.70 [0.45, 30.31]			
Ranaee 2024 0.2214355 0.173941 17.4% 1.25 [0.89, 1.76] Subtoal [6% C] 41.9% 2.14 [0.14, 4.52] Heterogeneity: Tau" = 0.40; Ch" = 14.04, df = 3 (P = 0.003); I" = 79% Test for overall effect: Z = 1.89 (P = 0.05) 1.2.2 Western countries Li 2017 ER-HER2: 0.65752 0.418257 8.9% 1.93 [0.85, 4.38] Li 2017 TNBC 0.46107562 0.208975 15.9% 1.57 [1.04, 2.37] Okcu 2021 0.11332669 0.445042 8.3% 1.12 [0.47, 2.66] Ozar 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Ozarowski 2021 0.01; Ch" = 5.06, df = 5 (P = 0.41); I" = 1% Test for overall effect: Z = 3.78 (P = 0.002) Total (95% C] Heterogeneity: Tau" = 0.00; Ch" = 5.06, df = 5 (P = 0.61); I" = 0.% C Study or Subgroup log[Hazard Ratio] SE Weight IV, Random .95% CI 1.3.1 $\geq$ 5 buds/HPF Sun 2014 0.4167347 0.371787 10.2% 1.52 [0.73, 3.14] Li 2017 TNBC 0.45107562 0.208975 15.9% 1.57 [1.04, 2.37] Mozarowski 2021 0.11332669 0.445042 8.3% 1.12 [0.47, 2.68] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Ranaee 2024 0.227002714 0.381858 9.9% Li 2017 TNBC 0.45107562 0.208975 15.9% 1.57 [1.04, 2.37] Mozarowski 2021 0.11332669 0.445042 8.3% 1.12 [0.47, 2.68] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Ranaee 2024 0.227012714 0.381858 9.9% 1.31 [0.62, 2.77] Subtotal (9% C) MOLT 0.1332869 0.445042 8.3% 1.12 [0.47, 2.68] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Ranaee 2024 0.227002714 0.381858 9.9% 1.31 [0.62, 2.77] Subtotal (9% C) MOLT 0.1332869 0.445042 8.3% 1.12 [0.47, 2.68] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Heterogeneity: Tau" = 0.00; Ch" = 5.47, df = 6 (P = 0.48); I" = 0% Test for overall effect: Z = 3.62 (P = 0.000) 1.3.2 $\geq$ 7 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Heterogeneity: Tau" = 0.00; Ch" = 5.47, df = 6 (P = 0.48); I" = 0% Test for overall effect: Z = 1.97 (P = 0.05) 1.3.3 $\geq$ 10 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Heterogeneity: Tau" = 0.00; Ch" = 5.47, df = 6 (P = 0.02); I" = 5.3% Test for overall effect: Z = 3.88 (P < 0.0001) Tot		Hou 2024	1.51446767	0.306644	12.3%	4.55 [2.49, 8.29]			
$ \begin{array}{c} \text{Subola (25.5 C)} & \text{Subola (25.7 C)} & \text$		Ranaee 2024	0.22314355	0.173941	17.4%	1.25 [0.89, 1.76]		-	
The let organise is the construction of the c		Heterogeneity: $Tau^2 = 1$	0.40 Chi <sup>2</sup> = 14.04 df	= 3 (P = 0	41.9%	2.14 [1.01, 4.52]			
<b>1.2.2</b> Western countries <b>1.2.2</b> Western countries <b>1.2.01</b> TERV-HER2- <b>0.65752</b> 0.418257 8.9% 1.93 [0.85, 4.38] <b>1.2.01</b> TNBC 0.45107562 0.208975 15.9% 1.57 [1.04, 2.37] Okcu 2021 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Mozarowski 2021 0.11332689 0.445042 8.3% 1.12 [0.47, 2.68] Ozen 2023 1.16627094 0.4019027 9.1% 3.22 [1.43, 7.18] Czer 2023 1.16627094 0.4019027 9.1% 3.22 [1.43, 7.18] Test for overall effect: $Z = 3.78$ (P = 0.0002) Total (95% Cl) 100.0 Ch <sup>2</sup> = 5.06 df = 5 (P = 0.41); P = 1% Test for overall effect: $Z = 3.78$ (P = 0.0001) Test for subarous differences: Ch <sup>2</sup> = 0.28, df = 1 (P = 0.60). P = 0% <b>C</b> <b>Study or Subgroup</b> log(Hazard Ratio) SE Weight IV. Random, 95% Cl <b>1.3.1</b> $\geq$ 5 buds/HPF Sun 2014 0.4167347 0.371787 10.2% 1.52 [0.73, 3.14] Li 2017 TNBC 0.45107562 0.208875 1.59% 1.57 [1.04, 2.37] Mozarowski 2021 0.11332689 0.445042 8.3% 1.12 [0.47, 2.68] Czer 2023 1.16627094 0.419627 9.1% 3.22 [1.43, 7.18] Ranaee 2024 0.22314355 0.173941 17.4% 1.25 [0.89, 1.76] Czer 2023 1.16627094 0.419627 9.1% 3.21 [1.43, 7.18] Ranaee 2024 0.22314355 0.173941 17.4% 1.25 [0.89, 1.76] Czer 2023 1.16627094 0.419627 9.1% 3.21 [1.43, 7.18] Ranaee 2024 0.22314355 0.173941 17.4% 1.25 [0.89, 1.76] Czer 2023 1.16627094 0.419627 9.1% 3.21 [1.43, 7.18] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5.47, df = 6 (P = 0.48); P = 0% Test for overall effect: Z = 1.37 (P = 0.05) <b>1.3.2</b> $\geq$ 7 buds/HPF Nicatuska 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 2.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Subtotal (95% Cl) 1.1346277 0.57653 5.9% 3.11 [1.00, 9.63] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 0.03; H = 0.02; P = 53% Test for overall effect: Z = 3.38 (P = 0.0001) Total (95% Cl) 1.0.01 P = 0.02; P = 53% Test for overall effect: Z = 3.38 (P = 0.0001)		Test for overall effect:	7 = 1.98 (P = 0.05)	- 3 (F - 0.	.003), 1	1970			
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		resciol overall effect.	L = 1.50 (1 = 0.00)						
Li 2017 ER-HER2- 0.65752 0.418257 8.9% 1.93 (0.85,4.38) Li 2017 TNBC 0.45107562 0.209875 15.9% 1.57 [1.04, 2.37] Okcu 2021 0.1132680 0.445042 8.3% 1.12 [0.47, 2.68] Ozer 2023 1.1662704 0.410927 9.1% 3.21 [1.43, 7.18] Czsen 2024 0.27002714 0.381858 9.9% 1.31 [0.62, 2.77] Subtotal (95% CI) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5.06, df = 5 (P = 0.41); P = 1% Test for overall effect: Z = 3.88 (P = 0.0001) Test for subbroud differences: Ch <sup>2</sup> = 0.28. df = 1 (P = 0.60). P = 0.9% C Study or Subgroup log[Hazard Ratio] SE Weight IV. Random, 95% CI V. Random, 95% CI 1.3.1 $\geq$ 5 buds/HPF Sun 2014 0.4167347 0.371787 10.2% 1.52 [0.73, 3.14] Li 2017 ER+HER2- 0.65752 0.418257 8.9% 1.93 [0.85, 4.38] Li 2017 TNBC 0.445107562 0.209875 15.9% 1.57 [1.04, 2.37] Mozarowski 2021 0.11322680 0.445042 8.3% 1.12 [0.47, 2.68] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Ranaee 2024 0.22314255 0.173941 1.74% 1.22 [0.89, 1.76] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Ranaee 2024 0.227002714 0.381858 9.9% 1.31 [0.62, 2.77] Subtotal (95% CI) 1.33690 0.45045 0.47594 0.410927 9.1% 3.21 [1.43, 7.18] Ranaee 2024 0.227002714 0.381858 9.9% 1.31 [0.62, 2.77] Subtotal (95% CI) 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Subtotal (95% CI) 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Subtotal (95% CI) 5.47, df = 6 (P = 0.48); P = 0% Test for overall effect: Z = 3.62 (P = 0.0003) 1.3.2 $\geq$ 7 buds/HPF Okcu 2021 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Subtotal (95% CI) 5.47, df = 6 (P = 0.48); P = 0% Test for overall effect: Z = 1.97 (P = 0.05) 1.3.3 $\geq$ 10 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5.47, df = 6 (P = 0.02); P = 53% Test for overall effect: Z = 5.08 (P = 0.0001) Total (95% CI) 10.00% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Ch <sup>2</sup> = 19.10, df = 9 (P = 0.02); P = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.8		1.2.2 Western countri	es						
L 2017 TNBC 0.45107562 0.208975 15.9% 1.57 [1.0.4, 2.37] Okcu 2021 1.13462273 0.57653 5.9% 3.11 [10.0, 9.63] Mozarowski 2021 0.11332869 0.445042 8.3% 1.12 [0.47, 2.68] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Ozer 2023 0.27002714 0.381858 9.9% 1.31 [0.62, 2.77] Subtotal (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.02; Ch <sup>2</sup> = 5.06, df = 5 (P = 0.02); P = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for suboroup log[Hazard Ratio] SE Weight IV. Random. 95% Cl 1.3.1 $\geq$ 5 buds/HPF Sun 2014 0.4167347 0.371787 10.2% 1.52 [0.73, 3.14] Li 2017 TNBC 0.45107562 0.209875 15.9% 1.97 [10.4, 2.37] Mozarowski 2021 0.1132569 0.445042 8.3% 1.12 [0.47, 2.68] Mozarowski 2021 0.132369 0.445042 8.3% 1.12 [0.47, 2.68] Mozarowski 2021 0.133269 0.445042 8.3% 1.12 [0.47, 2.68] Mozarowski 2021 0.133269 0.445042 8.3% 1.12 [0.47, 2.68] Mozarowski 2021 0.2314355 0.173941 17.4% 1.25 [0.89, 1.76] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Raneee 2024 0.22314355 0.173941 17.4% 1.25 [0.89, 1.76] Ozer 2024 0.2314355 0.173941 17.4% 1.25 [0.89, 1.76] Ozer 2024 0.2314355 0.173941 17.4% 1.25 [0.89, 1.76] Ozer 2024 0.2314355 0.173941 17.4% 1.48 [1.20, 1.82] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5.47, df = 6 (P = 0.08); P = 0% Test for overall effect: Z = 3.68 (P = 0.0001) Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Ch <sup>2</sup> = 19, 10, df = 9 (P = 0.02); P = 53%		Li 2017 ER+/HER2-	0.65752	0.418257	8.9%	1.93 [0.85, 4.38]			
$ \begin{array}{c} Okcu 2021 & 1.13462273 & 0.57653 & 5.9\% & 3.11 [1.00, 9.63] \\ Mozarowski 2021 & 0.1332686 & 0.445042 & 8.3\% & 1.12 [0.47, 2.66] \\ Ozer 2023 & 1.16627094 & 0.410927 & 9.1\% & 3.21 [1.43, 7.18] \\ Ozer 2024 & 0.27002714 & 0.381658 & 9.9\% & 1.31 [0.62, 2.77] \\ Subtotal (95\% C) & 58.1\% & 1.72 [1.30, 2.29] \\ Heterogeneity: Tau2 = 0.02; Chi2 = 5.6, df = 5 (P = 0.41); P = 1\% \\ Test for overall effect: Z = 3.76 (P = 0.0002) \\ \mathsf{Total (95\% C) & 100.0\% & 1.89 [1.37, 2.60] \\ Heterogeneity: Tau2 = 0.12; \mathsf{Chi2 = 19.10, df = 9 (P = 0.02); P = 53\% \\ Test for overall effect: Z = 3.88 (P = 0.0001) \\ \mathsf{Test for subaroup differences: \mathsf{Chi2 = 0.28. df = 1 (P = 0.60). P = 0.6 \\ Study or Subgroup  logHazard Ratio & Mazard Ratio \\ I.3.1 \approx 5 budyroup  logHazard Ratio & SE Weight \ IV. Random, 95\% Cl & IV. Random, 95\% Cl \\ I.3.1 \approx 5 Dudyroup  logHazard Ratio & I.52 [0.73, 3.14] \\ \mathsf{Li 2017 ER+MER2- & 0.65752 & 0.418257 & 8.9\% & 1.93 [0.85, 4.38] \\ Li 2017 TNBC & 0.450752 & 0.2418257 & 8.9\% & 1.57 [1.04, 2.37] \\ Mozarowski 2021 & 0.11332869 & 0.445042 & 8.3\% & 1.12 [0.47, 2.68] \\ Ozer 2023 & 1.16627094 & 0.410927 & 9.1\% & 3.21 [1.43, 7.18] \\ Ranaee 2024 & 0.227002714 & 0.381858 & 9.9\% & 1.31 [0.62, 2.77] \\ Subtotal (95\% C) & 7.98\% & 1.31 [0.62, 2.77] \\ Subtotal (95\% C) & 7.98\% & 1.11 [1.00, 9.63] \\ Subtotal (95\% C) & 1.13462273 & 0.57653 & 5.9\% & 3.11 [1.00, 9.63] \\ Heterogeneity: Tau2 = 0.00; Ch^2 = 5.47, df = 6 (P = 0.48); P = 0\% \\ Test for overall effect: Z = 3.82 (P = 0.0003) \\ \mathsf{1.3.2 \geq 7  buds/HPF \\ Hiratsuka 2022 & 1.30833282 & 1.073048 & 2.1\% & 3.70 [0.45, 30.31] \\ Hou 2024 & 1.51446767 & 0.306644 & 12.3\% & 4.55 [2.49, 8.29] \\ Subtotal (95\% C) & 1.0484767 & 0.306644 & 12.3\% & 4.55 [2.49, 8.29] \\ Fet for overall effect: Z = 1.97 (P = 0.05) \\ \mathsf{Tat for overall effect: Z = 3.68 (P = 0.0001) \\ \mathsf{Total (95\% C) & 10.00\% & 1.89 [1.37, 2.60] \\ Heterogeneity: Tau2 = 0.02; Ch^2 = 9 (0.001) \mathbb{P} =$		Li 2017 TNBC	0.45107562	0.209875	15.9%	1.57 [1.04, 2.37]		-	
$ \begin{array}{c cccc} Mozarowski 2021 & 0.11332869 0.445042 8.3% 1.12 [0.47, 2.68] \\ Ozer 2023 & 1.16627049 0.410927 9.1% 3.21 [1.43, 7.18] \\ Ozer 2024 & 0.27002714 0.381858 9.9% 1.31 [0.62, 2.77] \\ Subtotal (95% CI) & 58.1% 1.72 [1.30, 2.29] \\ Heterogenetiy: Tau2 = 0.00; Chi2 = 5.06, df = 5 (F = 0.41); F = 1\%Test for overall effect: Z = 3.88 (F = 0.0001)Test for overall effect: Z = 3.88 (F = 0.0001)Test for subgroup log[Hazard Ratio] SE Weight IV. Random, 95% CI1.3.1 \geq 5 buds/HPFSun 2014 0.4167347 0.371787 10.2\% 1.52 [0.73, 3.14] \\ Li 2017 TNBC 0.45107562 0.429975 15.9% 1.57 [1.04, 2.37] \\ Mozarowski 2021 0.11332869 0.445042 8.3% 1.12 [0.47, 2.68] \\ Ozer 2023 1.16827094 0.410927 9.1% 3.21 [1.43, 7.18] \\ Ranaee 2024 0.22314355 0.173941 17.4% 1.25 [0.89, 1.76] \\ Ozer 2024 0.227002714 0.381868 9.9% 1.31 [0.62, 2.77] \\ Subtotal (95% CI) 1.3.3 \geq 7 buds/HPFMeterogeneity: Tau2 = 0.00; Chi2 = 5.47, df = 6 (F = 0.48); F = 0\%Test for overall effect: Z = 1.62 (F = 0.003)1.3.2 \geq 7 buds/HPFMeterogeneity: Tau2 = 0.00; Chi2 = 5.47, df = 6 (F = 0.48); F = 0\%Test for overall effect: Z = 1.62 (F = 0.003)1.3.2 \geq 7 buds/HPFMicrosupative for the splicableTest for overall effect: Z = 1.62 (F = 0.003)1.3.2 \geq 7 buds/HPFHierogeneity: Not applicableTest for overall effect: Z = 1.97 (F = 0.03, df = 1 (F = 0.02); F = 5.3\%Test for overall effect: Z = 1.00; Chi2 = 0.003, df = 1 (F = 0.02); F = 0\%Test for overall effect: Z = 1.00; Chi2 = 0.003, df = 1 (F = 0.02); F = 0\%Test for overall effect: Z = 1.00; Chi2 = 0.003, df = 1 (F = 0.02); F = 0\%Test for overall effect: Z = 1.00; Chi2 = 0.003, df = 1 (F = 0.02); F = 0\%Test for overall effect: Z = 1.38 (F = 0.0001)Total (95% CI)Total (95% CI)$		Okcu 2021	1.13462273	0.57653	5.9%	3.11 [1.00, 9.63]			
Core 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Core 2024 0.27002714 0.381858 9.9% 1.72 [1.30, 2.29] Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 5.06, df = 5 (P = 0.41); P = 1% Test for overall effect: Z = 3.78 (P = 0.0002) Total (95% Cl) 10.0 ff = 9 (P = 0.02); P = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for subgroup log(Hazard Ratio) SE Weight IV. Random, 95% Cl IV.		Mozarowski 2021	0.11332869	0.445042	8.3%	1.12 [0.47, 2.68]			
$\begin{array}{c} 0.258 \text{ m} 2.024 & 0.2702/14 & 0.381858 & 9.9\% & 1.72 [1.30, 2.29] \\ \text{Heterogeneity: Tau" = 0.00; Ch" = 5.06, df = 5 (P = 0.41); P = 1\% \\ \text{Test for overall effect: Z = 3.78 (P = 0.0002) \\ \hline \text{Total (95\% CI)} & 100.0\% & 1.89 [1.37, 2.60] \\ \text{Heterogeneity: Tau" = 0.12; Ch" = 19.10, df = 9 (P = 0.02); P = 53\% \\ \text{Test for overall effect: Z = 3.88 (P = 0.0001) \\ \text{Test for subcroup differences: Ch" = 0.28, df = 1 (P = 0.60), P = 0\% \\ \hline \text{Mazard Ratio} & \text{Mazard Ratio} \\ \hline \text{Study or Subgroup log[Hazard Ratio]} & \text{SE Weight IV. Random, 95\% CI } \\ \hline \text{Mazard Ratio} & \text{Mazard Ratio} \\ \text{Study or Subgroup log[Hazard Ratio]} & \text{SE Weight IV. Random, 95\% CI } \\ \hline \text{Mazard Ratio} & \text{Mazard Ratio} \\ \text{IV. Random, 95\% CI } \\ \hline \text{Mazard Ratio} & \text{Mazard Ratio} \\ \text{Mazard Ratio} & \text{Matard Ratio} \\ Mazard R$		Ozer 2023	1.16627094	0.410927	9.1%	3.21 [1.43, 7.18]			
$ \begin{array}{c} \text{C} & \text$		Ozsen 2024 Subtotal (95% CI)	0.27002714	0.381858	9.9% 58.1%	1.31 [0.62, 2.77]		•	
Test for overall effect: $Z = 3.78 (P = 0.0002)$ Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); P = 53% Test for overall effect: $Z = 3.88 (P = 0.0001)$ Test for subaroup differences: Chi <sup>2</sup> = 0.28, df = 1 (P = 0.60). P = 0% C Hazard Ratio Hazard Ratio ISE Weight IV. Random, 95% Cl IV. Rand		Heterogeneity: $Tau^2 = 1$	0.00: Chi <sup>2</sup> = 5.06. df :	= 5 (P = 0.4	$(1):  ^2 = 1\%$	1.72 [1.00, 2.20]		· · ·	
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); I <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for subaroup differences: Chi <sup>2</sup> = 0.28, df = 1 (P = 0.60). I <sup>2</sup> = 0% C Study or Subgroup log[Hazard Ratio] SE Weight IV. Random. 95% CI 1.3.1 $\geq$ 5 buds/HPF Sun 2014 Li 2017 TNBC 0.4167347 0.371787 10.2% 1.32 [0.73, 3.14] Li 2017 TNBC 0.45752 0.418257 8.9% 1.39 [0.85, 4.38] Li 2017 TNBC 0.45752 0.418257 8.9% 1.59% 1.57 [1.04, 2.37] Mozarowski 2021 0.11332669 0.445042 8.3% 1.12 [0.47, 2.68] Ozer 2023 0.267294 0.4010927 9.1% 3.21 [1.43, 7.18] Ranaee 2024 0.22314355 0.173941 17.4% 1.25 [0.89, 1.76] Ozer 2023 0.27002714 0.381858 9.9% 1.31 [0.62, 2.77] Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 (P = 0.48); I <sup>2</sup> = 0% Test for overall effect: Z = 1.97 (P = 0.05) 1.3.3 $\geq$ 10 buds/HPF Hiratsuka 2022 1.08033282 1.073048 2.1% 3.70 [0.45, 30.31] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.3, df = 1 (P = 0.85); I <sup>2</sup> = 0% Test for overall effect: Z = 5.08 (P < 0.0001) Total (95% CI) 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% CI) Total (95% CI) 1.60 0.05; (1.4449 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% CI) Total (95% CI) 1.60 0.05; (1.4449 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% CI) Total (95% CI) 1.60 0.05; (1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); I <sup>2</sup> = 53% Test for overall effect: Z = 5.38 (P = 0.0001) Total (95% CI) 1.53 0 Duds/HPF Hiratsuka 2022 1.53 0 Did (P = 0.000; Chi <sup>2</sup> = 0.0001) Total (95% CI) 1.53 0 P = 0.0001 Total (95% CI) 1.53 0 P = 0.0001 Total (95% CI) 1.53 0 P = 0.0001) Test for overall effect: Z = 3.38 (P = 0.0001) Test for overall effect: Z = 3.38 (P = 0.0001) Test for overall effect: Z = 3.38 (P = 0.0001) Test for overall effect: Z = 3.38 (P = 0.0001) Test for overall effect: Z = 3.38 (P = 0.0001) Test for overall effect: Z = 3.38 (P = 0.0001) Test for overall effect: Z = 3.		Test for overall effect: 2	Z = 3.78 (P = 0.0002)	)	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,				
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Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for subgroup log[Hazard Ratio] SE Weight IV. Random. 95% Cl 1.3.1 $\geq$ 5 buds/HPF Sun 2014 0.4167347 0.371787 10.2% 1.52 [0.73, 3.14] Li 2017 ER-/HER2- 0.65752 0.418257 8.9% 1.93 [0.85, 4.38] Li 2017 TNBC 0.45107562 0.209875 15.9% 1.57 [1.04, 2.37] Mozarowski 2021 0.11332869 0.445042 8.3% 1.72 [0.47, 2.68] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Ranaee 2024 0.220131355 0.173941 17.4% 1.25 [0.89, 1.76] Ozers 2024 0.27002714 0.381858 9.9% 1.31 [1.00, 9.63] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 (P = 0.48); l <sup>2</sup> = 0% Test for overall effect: Z = 3.62 (P = 0.003) 1.3.2 $\geq$ 7 buds/HPF Okcu 2021 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Subtotal (95% Cl) 5.9% 3.11 [1.00, 9.63] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 (P = 0.48); l <sup>2</sup> = 0% Test for overall effect: Z = 1.97 (P = 0.05) 1.3.3 $\geq$ 10 buds/HPF Hiratsuka 2022 1.3083282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 1.144767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 1.1346277 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 1.13083282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 1.144767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 1.144767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 1.13083282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 1.514677 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 0.5 0.2 1 5 20 Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.		Total (95% CI)			100.0%	1.89 [1.37, 2.60]			
Test for overall effect: $Z = 3.88$ ( $P = 0.0001$ ) Test for subaroup differences: Chi <sup>2</sup> = 0.28. df = 1 ( $P = 0.60$ ). I <sup>2</sup> = 0% C Study or Subgroup log[Hazard Ratio] SE Weight IV. Random, 95% CI IV. Random, 95% CI 1.3.1 $\ge$ 5 buds/HPF Sun 2014 0.4167347 0.371787 10.2% 1.52 [0.73, 3.14] Li 2017 TNBC 0.45107562 0.209875 15.9% 1.57 [1.04, 2.37] Mozarowski 2021 0.11332869 0.445042 8.3% 1.12 [0.47, 2.68] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.16] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.16] Ozer 2024 0.2214355 0.173941 17.4% 1.25 [0.89, 1.76] Ozer 2024 0.27002714 0.381858 9.9% 1.31 [0.62, 2.77] Subtotal (95% CI) 79.8% 1.48 [1.20, 1.82] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 ( $P = 0.48$ ); I <sup>2</sup> = 0% Test for overall effect: Z = 3.62 ( $P = 0.0003$ ) 1.3.2 $\ge$ 7 buds/HPF Okcu 2021 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Subtotal (95% CI) 1.3383282 1.073048 2.1% 3.70 [0.45, 30.31] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 ( $P = 0.48$ ); I <sup>2</sup> = 0% Test for overall effect: Z = 1.97 ( $P = 0.05$ ) 1.3.3 $\ge$ 10 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.30664 12.3% 4.55 [2.49, 8.29] Subtotal (95% CI) 1.44% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 ( $P = 0.05$ ); I <sup>2</sup> = 0% Test for overall effect: Z = 5.08 ( $P < 0.00001$ ) Total (95% CI) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 ( $P = 0.02$ ); I <sup>2</sup> = 53% Test for overall effect: Z = 3.88 ( $P = 0.0001$ ) Total (95% CI) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.00, df = 9 ( $P = 0.02$ ); I <sup>2</sup> = 53% Test for overall effect: Z = 3.88 ( $P = 0.0001$ ) Test for overall effect: Z = 3.88 ( $P = 0.0001$ )		Heterogeneity: Tau <sup>2</sup> =	0.12; Chi <sup>2</sup> = 19.10, df	= 9 (P = 0.	.02); I <sup>2</sup> = 5	3%	0.05	0.2 1 5	20
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C Hazard Ratio Hazard Ratio Hazard Ratio Hazard Ratio Hazard Ratio Hazard Ratio UN Random, 95% Cl N.		rest for subaroup diffe	ronooo: Chi2 - 0.20	<b></b>	1 - 1 - 1 - 1				
Study or Subgroup       log[Hazard Ratio]       SE       Weight       IV. Random, 95% Cl       IV. Random, 95% Cl         1.3.1 ≥ 5 buds/HPF       0.4167347       0.371787       10.2%       1.52 [0.73, 3.14]         Li 2017 ER+/HER2-       0.65752       0.418257       8.9%       1.93 [0.85, 4.38]         Li 2017 TNBC       0.45107562       0.209875       15.9%       1.57 [1.04, 2.37]         Mozarowski 2021       0.11332869       0.445042       8.3%       1.12 [0.47, 2.68]         Ozer 2023       1.1662709 0.4040927       9.1%       3.21 [1.43, 7.18]         Ranaee 2024       0.22012714       0.381858       9.9%       1.31 [0.62, 2.77]         Subtotal (95% Cl)       79.8%       1.48 [1.20, 1.82]         Heterogeneily: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 (P = 0.48); l <sup>2</sup> = 0%       79.8%       3.11 [1.00, 9.63]         Subtotal (95% Cl)       5.9%       3.11 [1.00, 9.63]       1.32 ≥ 7 buds/HPF         Heterogeneily: Not applicable       5.9%       3.11 [1.00, 9.63]       1.32 ≥ 7 buds/HPF         Heterogeneily: Not applicable       1.51446767       0.306644       12.3%       4.55 [2.49, 8.29]         Subtotal (95% Cl)       1.44%       4.48 [2.51, 7.98]			rences: Chi <sup>2</sup> = 0.28. (	f = 1 (P = 0)	5.667.1	0%			
1.3.1 ≥ 5 buds/HPF Sun 2014 0.4167347 0.371787 10.2% 1.52 [0.73, 3.14] Li 2017 ER+/HER2- 0.65752 0.418257 8.9% 1.93 [0.85, 4.38] Li 2017 TNBC 0.45107562 0.209875 15.9% 1.57 [1.04, 2.37] Mozarowski 2021 0.11332869 0.445042 8.3% 1.12 [0.47, 2.68] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Ranaee 2024 0.22314355 0.173941 17.4% 1.25 [0.89, 1.76] Ozsen 2024 0.27002714 0.381858 9.9% 1.31 [0.62, 2.77] Subtotal (95% Cl) 79.8% 1.48 [1.20, 1.82] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 (P = 0.48); I <sup>2</sup> = 0% Test for overall effect: Z = 1.97 (P = 0.003) 1.3.2 ≥ 7 buds/HPF Hiratsuka 2022 1.3083282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 14.4% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); I <sup>2</sup> = 0% Test for overall effect: Z = 3.88 (P = 1.000) 1 Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); I <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); I <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); I <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = 0.0001)	с		rences: Chi <sup>2</sup> = 0.28. d	1 = 1 (P = 0	5.00 / 1	Hazard Ratio		Hazard Ratio	
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Li 2017 EIX/IEEZ <sup>2</sup> 0.000742 0.410237 0.5765 15.9% 1.57 [1.04, 2.37] Mozarowski 2021 0.11332869 0.445042 8.3% 1.12 [0.47, 2.68] Ozer 2023 1.16627094 0.410927 9.1% 3.21 [1.43, 7.18] Ranaee 2024 0.22314355 0.173941 17.4% 1.25 [0.89, 1.76] Ozsen 2024 0.27002714 0.381858 9.9% 1.31 [0.62, 2.77] Subtotal (95% CI) 79.8% 1.48 [1.20, 1.82] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 (P = 0.48); l <sup>2</sup> = 0% Test for overall effect: Z = 3.62 (P = 0.0003) 1.3.2 $\ge$ 7 buds/HPF Okcu 2021 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Subtotal (95% CI) 5.9% 3.11 [1.00, 9.63] Heterogeneity: Not applicable Test for overall effect: Z = 1.97 (P = 0.05) 1.3.3 $\ge$ 10 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% CI) 14.4% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: Z = 5.08 (P < 0.00001) Total (95% CI) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Total (95% CI) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.60 df = 2 (P = 0.001) l <sup>2</sup> = 85 3%	C	Study or Subgroup 1.3.1 ≥ 5 buds/HPF	rences: Chi <sup>2</sup> = 0.28. d	SE	Weight	Hazard Ratio IV. Random, 95% CI		Hazard Ratio IV. Random. 95% CI	
$\begin{array}{c} \text{Hoth first} & Hoth $	C	Study or Subgroup $1.3.1 \ge 5$ buds/HPF Sun 2014 1.2014 = EP+/HEP2	rences: Chi <sup>2</sup> = 0.28. ( log[Hazard Ratio] 0.4167347 0.65752	0.371787	Weight 10.2%	Hazard Ratio <u>IV. Random, 95% CI</u> 1.52 [0.73, 3.14]		Hazard Ratio IV. Random, 95% CI	
Ozer 2023       1.16627094       0.410927       9.1%       3.21 [1.43, 7.18]         Ranaee 2024       0.22314355       0.173941       17.4%       1.25 [0.89, 1.76]         Ozsen 2024       0.27002714       0.381858       9.9%       1.31 [0.62, 2.77]         Subtotal (95% CI)       79.8%       1.48 [1.20, 1.82]         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 (P = 0.48); l <sup>2</sup> = 0%         Test for overall effect: Z = 3.62 (P = 0.0003) <b>1.3.2</b> ≥ 7 buds/HPF         Okcu 2021       1.13462273       0.57653       5.9%       3.11 [1.00, 9.63]         Subtotal (95% CI)       5.9%       3.11 [1.00, 9.63]         Heterogeneity: Not applicable       5.9%       3.11 [1.00, 9.63]         Test for overall effect: Z = 1.97 (P = 0.05)       1.3.3 ≥ 10 buds/HPF         Hiratsuka 2022       1.30833282       1.073048       2.1%       3.70 [0.45, 30.31]         Hou 2024       1.51446767       0.306644       12.3%       4.55 [2.49, 8.29]         Subtotal (95% CI)       14.4%       4.48 [2.51, 7.98]       4.55 [2.49, 8.29]         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0%       0.05       0.2       1       5       20         Total (95% CI)       100.0%       1.89 [1.37, 2.60]       0.05	C	Study or Subgroup 1.3.1 $\geq$ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC	rences: Chi <sup>2</sup> = 0.28. d log[Hazard Ratio] 0.4167347 0.65752 0.45107562	0.371787 0.418257 0.209875	Weight 10.2% 8.9% 15.9%	Hazard Ratio <u>IV. Random, 95% CI</u> 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37]		Hazard Ratio	
Ranaee 2024 0.22314355 0.173941 17.4% 1.25 [0.89, 1.76] Ozsen 2024 0.27002714 0.381858 9.9% 1.31 [0.62, 2.77] Subtotal (95% Cl) 79.8% 1.48 [1.20, 1.82] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 (P = 0.48); l <sup>2</sup> = 0% Test for overall effect: Z = 3.62 (P = 0.0003) 1.3.2 ≥ 7 buds/HPF Okcu 2021 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Subtotal (95% Cl) 5.9% 3.11 [1.00, 9.63] Heterogeneity: Not applicable Test for overall effect: Z = 1.97 (P = 0.05) 1.3.3 ≥ 10 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 14.4% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: Z = 5.08 (P < 0.00001) Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.88 (P = 0.0001)	C	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021	rences: Chi <sup>2</sup> = 0.28. ( log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869	0.371787 0.418257 0.445042	Weight 10.2% 8.9% 15.9% 8.3%	Hazard Ratio <u>IV, Random, 95% CI</u> 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1 12 [0 47, 2 68]		Hazard Ratio	
Ozsen 2024 0.27002714 0.381858 9.9% 1.31 [0.62, 2.77] Subtotal (95% Cl) 79.8% 1.48 [1.20, 1.82] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 (P = 0.48); l <sup>2</sup> = 0% Test for overall effect: Z = 3.62 (P = 0.0003) 1.3.2 $\ge$ 7 buds/HPF Okcu 2021 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Subtotal (95% Cl) 5.9% 3.11 [1.00, 9.63] Heterogeneity: Not applicable Test for overall effect: Z = 1.97 (P = 0.05) 1.3.3 $\ge$ 10 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 14.4% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: Z = 5.08 (P < 0.00001) Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.88 (P = 0.0001) Test for overall effect: Z = 3.88 (P = 0.0001)	C	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023	rences: Chi <sup>2</sup> = 0.28. d log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094	0.371787 0.418257 0.209875 0.445042 0.410927	Weight 10.2% 8.9% 15.9% 8.3% 9.1%	Hazard Ratio <u>IV, Random, 95% CI</u> 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18]		Hazard Ratio	
Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 (P = 0.48); l <sup>2</sup> = 0% Test for overall effect: $Z = 3.62$ (P = 0.0003) 1.3.2 $\ge$ 7 buds/HPF Okcu 2021 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Subtotal (95% Cl) 5.9% 3.11 [1.00, 9.63] Heterogeneity: Not applicable Test for overall effect: $Z = 1.97$ (P = 0.05) 1.3.3 $\ge$ 10 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 14.4% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: $Z = 5.08$ (P < 0.00001) Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001)	C _	Study or Subgroup           1.3.1 ≥ 5 buds/HPF           Sun 2014           Li 2017 ER+/HER2-           Li 2017 TNBC           Mozarowski 2021           Ozer 2023           Ranaee 2024	rences: Chi <sup>2</sup> = 0.28. d log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355	0.371787 0.418257 0.209875 0.445042 0.445042 0.440927 0.173941	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4%	Hazard Ratio <u>IV. Random, 95% CI</u> 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76]		Hazard Ratio IV. Random. 95% CI	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.47, df = 6 (P = 0.48); l <sup>2</sup> = 0% Test for overall effect: $Z = 3.62$ (P = 0.0003) <b>1.3.2</b> $\ge$ 7 buds/HPF Okcu 2021 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Subtotal (95% Cl) 5.9% 3.11 [1.00, 9.63] Heterogeneity: Not applicable Test for overall effect: $Z = 1.97$ (P = 0.05) <b>1.3.3</b> $\ge$ 10 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 14.4% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: $Z = 5.08$ (P < 0.00001) Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001)	C	Study or Subgroup           1.3.1 ≥ 5 buds/HPF           Sun 2014           Li 2017 ER+/HER2-           Li 2017 TNBC           Mozarowski 2021           Ozer 2023           Ranaee 2024           Ozsen 2024	rences: Chi <sup>2</sup> = 0.28. d log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714	0.371787 0.418257 0.209875 0.445042 0.445042 0.410927 0.173941 0.381858	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 9.9%	Hazard Ratio IV. Random. 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77]		Hazard Ratio	
Test for overall effect: $Z = 3.62$ (P = 0.0003) 1.3.2 $\ge$ 7 buds/HPF Okcu 2021 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Subtotal (95% Cl) 5.9% 3.11 [1.00, 9.63] Heterogeneity: Not applicable Test for overall effect: $Z = 1.97$ (P = 0.05) 1.3.3 $\ge$ 10 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 14.4% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: $Z = 5.08$ (P < 0.00001) Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for overall effect: $Z = 3.88$ (P = 0.0001)	C	Study or Subgroup           1.3.1 ≥ 5 buds/HPF           Sun 2014           Li 2017 ER+/HER2-           Li 2017 TNBC           Mozarowski 2021           Ozer 2023           Ranaee 2024           Ozsen 2024           Subtotal (95% CI)	rences: Chi <sup>2</sup> = 0.28. d log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.41332869 1.16627094 0.22314355 0.27002714	SE 0.371787 0.418257 0.209875 0.445042 0.445042 0.410927 0.173941 0.381858	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 9.9% 79.8%	Hazard Ratio IV. Random. 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82]		Hazard Ratio	
1.3.2 ≥ 7 buds/HPF Okcu 2021 1.13462273 0.57653 5.9% 3.11 [1.00, 9.63] Subtotal (95% Cl) 5.9% 3.11 [1.00, 9.63] Heterogeneity: Not applicable Test for overall effect: $Z = 1.97$ (P = 0.05) 1.3.3 ≥ 10 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 14.4% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: $Z = 5.08$ (P < 0.00001) Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for subgroup differences: Chi <sup>2</sup> = 13.60 df = 2 (P = 0.001), l <sup>2</sup> = 85.3%	C	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> =	rences: Chi <sup>2</sup> = 0.28. d log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.41332869 1.16627094 0.22314355 0.27002714 0.00; Chi <sup>2</sup> = 5.47, df =	0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 9.9% 79.8% (8);   <sup>2</sup> = 0%	Hazard Ratio IV. Random. 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82]		Hazard Ratio	
Okcu 2021       1.13462273       0.57653       5.9%       3.11 [1.00, 9.63]         Subtotal (95% Cl)       5.9%       3.11 [1.00, 9.63]         Heterogeneity: Not applicable       7.9%       3.11 [1.00, 9.63]         Test for overall effect: Z = 1.97 (P = 0.05)       1.3.3 $\geq$ 10 buds/HPF         Hiratsuka 2022       1.30833282       1.073048       2.1%       3.70 [0.45, 30.31]         Hou 2024       1.51446767       0.306644       12.3%       4.55 [2.49, 8.29]         Subtotal (95% Cl)       14.4%       4.48 [2.51, 7.98]         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0%       Test for overall effect: Z = 5.08 (P < 0.00001)         Total (95% Cl)       100.0%       1.89 [1.37, 2.60]         Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53%       0.05       0.2         Test for overall effect: Z = 3.88 (P = 0.0001)       0.05       0.2       1       5       20         Test for subroup differences: Chi <sup>2</sup> = 13.60 df = 2 (P = 0.001) l <sup>2</sup> = 85.3%       1       5       20       1       5       20	C	Study or Subgroup1.3.1 ≥ 5 buds/HPFSun 2014Li 2017 ER+/HER2-Li 2017 TNBCMozarowski 2021Ozer 2023Ranaee 2024Ozsen 2024Subtotal (95% CI)Heterogeneity: Tau² =Test for overall effect: 2	rences: Chi <sup>2</sup> = 0.28. ( log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; Chi <sup>2</sup> = 5.47, df = Z = 3.62 (P = 0.0003)	0.371787 0.418257 0.209875 0.445042 0.419027 0.173941 0.381858 = 6 (P = 0.4	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 9.9% 79.8% (88); l <sup>2</sup> = 0%	Hazard Ratio IV. Random. 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82]		Hazard Ratio IV. Random. 95% CI	
Subtotal (95% Cl) 5.9% 3.11 [1.00, 9.63] Heterogeneity: Not applicable Test for overall effect: $Z = 1.97$ (P = 0.05) 1.3.3 $\geq$ 10 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 14.4% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: $Z = 5.08$ (P < 0.00001) Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for overall effect: $Z = 3.88$ (P = 0.0001) Test for subgroup differences: Chi <sup>2</sup> = 13.60 df = 2 (P = 0.001) l <sup>2</sup> = 85.3%	C	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect 3 1.3.2 ≥ 7 buds/HPF	rences: Chi <sup>2</sup> = 0.28. ( log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; Chi <sup>2</sup> = 5.47, df = Z = 3.62 (P = 0.0003)	st = 1 (P = ( <u>SE</u> 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 9.9% 79.8% (8);   <sup>2</sup> = 0%	Hazard Ratio IV. Random, 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82]		Hazard Ratio IV. Random. 95% CI	
Heterogeneity: Not applicable Test for overall effect: $Z = 1.97 (P = 0.05)$ 1.3.3 $\geq$ 10 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 14.4% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: $Z = 5.08 (P < 0.00001)$ Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for overall effect: $Z = 3.88 (P = 0.0001)$ Test for overall effect: $Z = 3.88 (P = 0.0001)$ Test for subgroup differences: Chi <sup>2</sup> = 13.60 df = 2 (P = 0.001) l <sup>2</sup> = 85.3%	C .	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect 3 1.3.2 ≥ 7 buds/HPF Okcu 2021	rences: Chi <sup>2</sup> = 0.28. d log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; Chi <sup>2</sup> = 5.47, df Z = 3.62 (P = 0.0003) 1.13462273	SE 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 9.9% 79.8% (8);   <sup>2</sup> = 0%	Hazard Ratio IV. Random, 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82] 3.11 [1.00, 9.63]		Hazard Ratio IV. Random. 95% CI	
Test for overall effect: $Z = 1.97 (P = 0.05)$ 1.3.3 $\geq 10$ buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 14.4% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: $Z = 5.08 (P < 0.00001)$ Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for subgroup differences: Chi <sup>2</sup> = 13.60 df = 2 (P = 0.001) l <sup>2</sup> = 85.3%	C .	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozer 2024 Czsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 1.3.2 ≥ 7 buds/HPF Okcu 2021 Subtotal (95% CI)	rences: Chi <sup>2</sup> = 0.28. d log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; Chi <sup>2</sup> = 5.47, df = Z = 3.62 (P = 0.0003) 1.13462273	st = 1 (P = ( SE 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4 0.57653	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 9.9% 79.8% 79.8% (8);   <sup>2</sup> = 0% 5.9% 5.9%	Hazard Ratio IV. Random, 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63]		Hazard Ratio IV. Random. 95% CI	
1.3.3 ≥ 10 buds/HPF Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 14.4% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: Z = 5.08 (P < 0.00001) Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for subgroup differences: Chi <sup>2</sup> = 13.60, df = 2 (P = 0.001) l <sup>2</sup> = 85.3%	C	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 1.3.2 ≥ 7 buds/HPF Okcu 2021 Subtotal (95% CI) Heterogeneity: Not app	rences: Chi <sup>2</sup> = 0.28. d log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; Chi <sup>2</sup> = 5.47, df = Z = 3.62 (P = 0.0003) 1.13462273 blicable	st = 1 (P = ( SE 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4 ) 0.57653	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 9.9% 79.8% 79.8% 88); l <sup>2</sup> = 0% 5.9% 5.9%	Hazard Ratio IV. Random, 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63]		Hazard Ratio IV. Random. 95% CI	
1.3.3 $\leq$ 10 DUBS/HPF         Hiratsuka 2022       1.30833282       1.073048       2.1%       3.70 [0.45, 30.31]         Hou 2024       1.51446767       0.306644       12.3%       4.55 [2.49, 8.29]         Subtotal (95% CI)       14.4%       4.48 [2.51, 7.98]         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0%         Test for overall effect: Z = 5.08 (P < 0.00001)         Total (95% CI)       100.0%       1.89 [1.37, 2.60]         Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53%       0.05       0.2         Test for overall effect: Z = 3.88 (P = 0.0001)       100.0%       1.89 [1.37, 2.60]         Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53%       0.05       0.2       1       5       20	c	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozsen 2024 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 1.3.2 ≥ 7 buds/HPF Okcu 2021 Subtotal (95% Cl) Heterogeneity: Not app Test for overall effect: 2	rences: Chi <sup>2</sup> = 0.28. d log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; Chi <sup>2</sup> = 5.47, df = Z = 3.62 (P = 0.0003) 1.13462273 blicable Z = 1.97 (P = 0.05)	st = 1 (P = ( SE 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4 ) 0.57653	Weight 10.2% 8.9% 15.9% 9.1% 17.4% 9.9% 79.8% (8);   <sup>2</sup> = 0% 5.9% 5.9%	Hazard Ratio IV. Random, 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63]		Hazard Ratio IV. Random. 95% CI	
Hiratsuka 2022 1.30833282 1.073048 2.1% 3.70 [0.45, 30.31] Hou 2024 1.51446767 0.306644 12.3% 4.55 [2.49, 8.29] Subtotal (95% Cl) 14.4% 4.48 [2.51, 7.98] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: Z = 5.08 (P < 0.00001) Total (95% Cl) 100.0% 1.89 [1.37, 2.60] Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for subgroup differences: Chi <sup>2</sup> = 13.60, df = 2 (P = 0.001) l <sup>2</sup> = 85.3%	C	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozsen 2024 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 1 1.3.2 ≥ 7 buds/HPF Okcu 2021 Subtotal (95% Cl) Heterogeneity: Not app Test for overall effect: 2 1.0.0 ≥ 100 + 100 - 1	rences: Chi <sup>2</sup> = 0.28. d log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; Chi <sup>2</sup> = 5.47, df 3 Z = 3.62 (P = 0.0003) 1.13462273 blicable Z = 1.97 (P = 0.05)	st = 1 (P = ( SE 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4 0.57653	Weight 10.2% 8.9% 15.9% 9.1% 9.9% 79.8% (8);   <sup>2</sup> = 0% 5.9% 5.9%	Hazard Ratio IV. Random. 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63]		Hazard Ratio IV. Random. 95% CI	
Find 2024       1.51440/67       0.306044       12.5%       4.35 [2.49, 6.29]         Subtotal (95% CI)       14.4%       4.48 [2.51, 7.98]         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0%         Test for overall effect: Z = 5.08 (P < 0.00001)         Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53%         Test for overall effect: Z = 3.88 (P = 0.0001)         Test for subroup differences: Chi <sup>2</sup> = 13.60, df = 2 (P = 0.001) l <sup>2</sup> = 85.3%	C	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozsen 2024 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 1 1.3.2 ≥ 7 buds/HPF Okcu 2021 Subtotal (95% Cl) Heterogeneity: Not app Test for overall effect: 2 1.3.3 ≥ 10 buds/HPF	rences: Chi <sup>2</sup> = 0.28. d log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; Chi <sup>2</sup> = 5.47, df : Z = 3.62 (P = 0.0003) 1.13462273 blicable Z = 1.97 (P = 0.05)	st = 1 (P = ( <u>SE</u> 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4 0.57653	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 9.9% 79.8% (8);   <sup>2</sup> = 0% 5.9% 5.9%	Hazard Ratio IV. Random. 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63]		Hazard Ratio IV. Random. 95% CI	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: Z = 5.08 (P < 0.00001) Total (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = 0.0001) Test for subgroup differences: Chi <sup>2</sup> = 13.60, df = 2 (P = 0.001) l <sup>2</sup> = 85.3%	C	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozsen 2024 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 1 1.3.2 ≥ 7 buds/HPF Okcu 2021 Subtotal (95% Cl) Heterogeneity: Not app Test for overall effect: 2 1.3.3 ≥ 10 buds/HPF Hiratsuka 2022 Her 2024	rences: Chi <sup>2</sup> = 0.28. ( log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; Chi <sup>2</sup> = 5.47, df 3 Z = 3.62 (P = 0.0003) 1.13462273 blicable Z = 1.97 (P = 0.05) 1.30833282 4.54446227	st = 1 (P = ( SE 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4) 0.57653 1.073048	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 9.9% 79.8% 88); l <sup>2</sup> = 0% 5.9% 5.9% 2.1% 12.2%	Hazard Ratio IV. Random. 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.70 [0.45, 30.31] 4.55 [0.40, 2.02]		Hazard Ratio	
Test for overall effect: $Z = 5.08$ (P < 0.00001)         Total (95% Cl)         Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53%         Test for overall effect: $Z = 3.88$ (P = 0.0001)         Test for subgroup differences: Chi <sup>2</sup> = 13.60, df = 2 (P = 0.001) l <sup>2</sup> = 85.3%	C	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 1.3.2 ≥ 7 buds/HPF Okcu 2021 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 1.3.3 ≥ 10 buds/HPF Hiratsuka 2022 Hou 2024 Subtotal (95% CI)	rences: Chi <sup>2</sup> = 0.28. ( log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; Chi <sup>2</sup> = 5.47, df = Z = 3.62 (P = 0.0003) 1.13462273 blicable Z = 1.97 (P = 0.05) 1.30833282 1.51446767	st = 1 (P = ( <u>SE</u> 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4) 0.57653 1.073048 0.306644	Weight 10.2% 8.9% 15.9% 9.1% 17.4% 9.9% 79.8% 18.8; l <sup>2</sup> = 0% 5.9% 5.9% 2.1% 12.3% 14.4%	Hazard Ratio IV. Random. 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.70 [0.45, 30.31] 4.55 [2.49, 8.29] 4.48 [2 51, 7 98]		Hazard Ratio	
Total (95% Cl)       100.0%       1.89 [1.37, 2.60]         Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% $0.05$ $0.2$ $1$ $5$ $20$ Test for overall effect: Z = 3.88 (P = 0.0001)       Test for subgroup differences: Chi <sup>2</sup> = 13.60, df = 2 (P = 0.001) $l2 = 85.3\%$ $0.05$ $0.2$ $1$ $5$ $20$	C	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 1.3.2 ≥ 7 buds/HPF Okcu 2021 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 3 1.3.3 ≥ 10 buds/HPF Hiratsuka 2022 Hou 2024 Subtotal (95% CI)	rences: Chi <sup>2</sup> = 0.28. d log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; Chi <sup>2</sup> = 5.47, df = Z = 3.62 (P = 0.0003) 1.13462273 blicable Z = 1.97 (P = 0.05) 1.30833282 1.51446767 0.00; Chi <sup>2</sup> = 0.03, df =	st = 1 (P = 0 SE 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4) 0.57653 1.073048 0.306644 = 1 (P = 0.8)	Weight           10.2%           8.9%           15.9%           8.3%           9.1%           17.4%           9.9%           79.8%           18); I² = 0%           5.9%           5.9%           2.1%           12.3%           14.4%           (5); I² = 0%	Hazard Ratio IV. Random. 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.70 [0.45, 30.31] 4.55 [2.49, 8.29] 4.48 [2.51, 7.98]		Hazard Ratio IV. Random. 95% CI	
Total (95% Cl)       100.0%       1.89 [1.37, 2.60]         Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = 0.02); l <sup>2</sup> = 53% $0.05$ $0.2$ $1$ $5$ $20$ Test for overall effect: Z = 3.88 (P = 0.0001)       Test for subgroup differences: Chi <sup>2</sup> = 13.60, df = 2 (P = 0.001) l <sup>2</sup> = 85.3% $0.05$ $0.2$ $1$ $5$ $20$	C .	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 1.3.2 ≥ 7 buds/HPF Okcu 2021 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 1.3.3 ≥ 10 buds/HPF Hiratsuka 2022 Hou 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 Heterogeneity: Tau <sup>2</sup> = 1 Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 Heterogeneity: Tau <sup>2</sup> = 1 Heterogeneity: Tau <sup>2</sup> = 1 Heterogeneity	rences: $Chi^2 = 0.28. c$ log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; $Chi^2 = 5.47, df = 2$ 2 = 3.62 (P = 0.0003) 1.13462273 blicable Z = 1.97 (P = 0.05) 1.30833282 1.51446767 0.00; $Chi^2 = 0.03, df = 2$ Z = 5.08 (P < 0.0000)	st = 1 (P = 0 SE 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4 0.57653 1.073048 0.306644 = 1 (P = 0.8 1)	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 79.8% 17.4% 79.8% 17.4% 5.9% 5.9% 5.9% 2.1% 12.3% 14.4% 15.9% 14.4%	Hazard Ratio IV. Random. 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.70 [0.45, 30.31] 4.55 [2.49, 8.29] 4.48 [2.51, 7.98]		Hazard Ratio IV. Random. 95% CI	
Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 19.10, df = 9 (P = $0.02$ ); l <sup>2</sup> = 53% Test for overall effect: Z = 3.88 (P = $0.0001$ ) Test for subgroup differences: Chi <sup>2</sup> = 13.60, df = 2 (P = $0.001$ ), l <sup>2</sup> = 85.3%	C.	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozsen 2024 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 1.3.2 ≥ 7 buds/HPF Okcu 2021 Subtotal (95% Cl) Heterogeneity: Not app Test for overall effect: 2 1.3.3 ≥ 10 buds/HPF Hiratsuka 2022 Hou 2024 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 1 Li 2024 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 Hou 2024 Subtotal (95% Cl)	rences: $Chi^2 = 0.28$ . ( log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; $Chi^2 = 5.47$ , df = Z = 3.62 (P = 0.0003) 1.13462273 blicable Z = 1.97 (P = 0.05) 1.30833282 1.51446767 0.00; $Chi^2 = 0.03$ , df = Z = 5.08 (P < 0.0000)	st = 1 (P = 0 SE 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4 0.57653 1.073048 0.306644 = 1 (P = 0.8 1)	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 79.8% 79.8% 8); l <sup>2</sup> = 0% 5.9% 5.9% 2.1% 12.3% 14.4% 15); l <sup>2</sup> = 0%	Hazard Ratio IV. Random. 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.70 [0.45, 30.31] 4.55 [2.49, 8.29] 4.48 [2.51, 7.98]		Hazard Ratio IV. Random. 95% CI	
Test for subgroup differences: $Chi^2 = 13.60$ , $df = 2$ (P = 0.001), $I^2 = 85.3\%$	C.	Study or Subgroup1.3.1 ≥ 5 buds/HPFSun 2014Li 2017 ER+/HER2-Li 2017 TNBCMozarowski 2021Ozer 2023Ranaee 2024Ozer 2024Subtotal (95% CI)Heterogeneity: Tau² = 1Test for overall effect: 21.3.2 ≥ 7 buds/HPFOkcu 2021Subtotal (95% CI)Heterogeneity: Not appTest for overall effect: 21.3.3 ≥ 10 buds/HPFHiratsuka 2022Hou 2024Subtotal (95% CI)Heterogeneity: Tau² = 1Test for overall effect: 2	rences: $Chi^2 = 0.28. c$ log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; $Chi^2 = 5.47, df = 2$ 2 = 3.62 (P = 0.0003) 1.13462273 blicable Z = 1.97 (P = 0.05) 1.30833282 1.51446767 0.00; $Chi^2 = 0.03, df = 2$ Z = 5.08 (P < 0.0000)	st = 1 (P = 0 SE 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4 0.57653 1.073048 0.306644 = 1 (P = 0.8 1)	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 9.9% 79.8% 8); I <sup>2</sup> = 0% 5.9% 5.9% 12.3% 14.4% 155); I <sup>2</sup> = 0%	Hazard Ratio IV. Random, 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.70 [0.45, 30.31] 4.55 [2.49, 8.29] 4.48 [2.51, 7.98] 4.89 [1.37, 2.60]		Hazard Ratio IV. Random. 95% CI	
	c	Study or Subgroup 1.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Mozarowski 2021 Ozer 2023 Ranaee 2024 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 1.3.2 ≥ 7 buds/HPF Okcu 2021 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 1.3.3 ≥ 10 buds/HPF Hiratsuka 2022 Hou 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Total (95% CI)	rences: $Chi^2 = 0.28. c$ log[Hazard Ratio] 0.4167347 0.65752 0.45107562 0.11332869 1.16627094 0.22314355 0.27002714 0.00; $Chi^2 = 5.47, df = 2$ 2 = 3.62 (P = 0.0003) 1.13462273 blicable Z = 1.97 (P = 0.05) 1.30833282 1.51446767 0.00; $Chi^2 = 0.03, df = 2$ Z = 5.08 (P < 0.0000) 0.12; $Chi^2 = 19.10, df = 2$	st = 1 (P = 0 SE 0.371787 0.418257 0.209875 0.445042 0.410927 0.173941 0.381858 = 6 (P = 0.4 0.57653 1.073048 0.306644 = 1 (P = 0.8 1) = 9 (P = 0.	Weight 10.2% 8.9% 15.9% 8.3% 9.1% 17.4% 9.9% 79.8% 8); l <sup>2</sup> = 0% 5.9% 5.9% 12.3% 14.4% 155); l <sup>2</sup> = 0% 100.0% 02); l <sup>2</sup> = 5	Hazard Ratio IV. Random, 95% CI 1.52 [0.73, 3.14] 1.93 [0.85, 4.38] 1.57 [1.04, 2.37] 1.12 [0.47, 2.68] 3.21 [1.43, 7.18] 1.25 [0.89, 1.76] 1.31 [0.62, 2.77] 1.48 [1.20, 1.82] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.11 [1.00, 9.63] 3.70 [0.45, 30.31] 4.55 [2.49, 8.29] 4.48 [2.51, 7.98] 4.89 [1.37, 2.60]		Hazard Ratio IV. Random. 95% CI	

Figure 2. Forest plots for the meta-analysis of the association between tumor budding and OS in patients with BC. (A) Forest plots for the overall meta-analysis; (B) Forest plots for the subgroup analysis according to the study country; (C) Forest plots for the subgroup analysis according to the cutoffs for defining a high tumor budding. BC: Breast cancer; OS: Overall survival.



Li 2017 ER+/HER2-	0.65752	0.418257	8.9%	1.93 [0.85, 4.38]			+-	_	
Okcu 2021	1.13462273	0.57653	5.9%	3.11 [1.00, 9.63]					
Mozarowski 2021	0.11332869	0.445042	8.3%	1.12 [0.47, 2.68]			-		
Hiratsuka 2022	1.30833282	1.073048	2.1%	3.70 [0.45, 30.31]					
Ozsen 2024	0.27002714	0.381858	9.9%	1.31 [0.62, 2.77]			+		
Subtotal (95% CI)			35.1%	1.65 [1.08, 2.51]			•		
Heterogeneity: Tau <sup>2</sup> = 0.00; C	hi² = 3.04, df :	= 4 (P = 0.5	5); I² = 0%						
Test for overall effect: Z = 2.3	1 (P = 0.02)								
Total (95% CI)			100.0%	1 89 [1 37 2 60]			•		
10(41 (3570 01)			100.070	1.05 [1.57, 2.00]					
Heterogeneity: Tau <sup>2</sup> = 0.12; C	;hi² = 19.10, df	f = 9 (P = 0.	02); I² = 53%	, ,	0.05	0.2	1	5	20
Test for overall effect: Z = 3.8	8 (P = 0.0001)	)			0.00	0.2		0	20
Test for subaroup differences	: Chi <sup>2</sup> = 0.41. d	df = 1 (P = 0)	).52). I <sup>2</sup> = 0%						

				Hazard Ratio		Hazard	l Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl		IV, Rando	m, 95% C	:
1.6.1 Multivariate an	nalysis							
Sun 2014	0.4167347	0.371787	10.2%	1.52 [0.73, 3.14]		-+	•	
Li 2017 ER+/HER2-	0.65752	0.418257	8.9%	1.93 [0.85, 4.38]		+	•	
Li 2017 TNBC	0.45107562	0.209875	15.9%	1.57 [1.04, 2.37]			-	
Okcu 2021	1.13462273	0.57653	5.9%	3.11 [1.00, 9.63]			•	_
Hiratsuka 2022	1.30833282	1.073048	2.1%	3.70 [0.45, 30.31]		-	•	
Hou 2024	1.51446767	0.306644	12.3%	4.55 [2.49, 8.29]			-	-
Subtotal (95% CI)			55.3%	2.27 [1.46, 3.53]			•	
Heterogeneity: Tau <sup>2</sup>	= 0.13; Chi <sup>2</sup> = 9.81, df =	= 5 (P = 0.0	8); I <sup>2</sup> = 49	%				
Test for overall effec	t: Z = 3.65 (P = 0.0003)	)						
1.6.2 Univariate ana	alysis							
Mozarowski 2021	0.11332869	0.445042	8.3%	1.12 [0.47, 2.68]			_	
Ozer 2023	1.16627094	0.410927	9.1%	3.21 [1.43, 7.18]				
Ranaee 2024	0.22314355	0.173941	17.4%	1.25 [0.89, 1.76]		1	•	
Ozsen 2024	0.27002714	0.381858	9.9%	1.31 [0.62, 2.77]				
Subtotal (95% CI)			44.7%	1.47 [0.98, 2.21]		ł	•	
Heterogeneity: Tau <sup>2</sup>	= 0.07; Chi <sup>2</sup> = 4.78, df =	= 3 (P = 0.1	9); I <sup>2</sup> = 37	%				
Test for overall effect	t: Z = 1.87 (P = 0.06)							
Total (95% Cl)			100.0%	1.89 [1.37, 2.60]			•	
Heterogeneity: Tau <sup>2</sup>	= 0.12; Chi <sup>2</sup> = 19.10, df	f = 9 (P = 0.	02); l <sup>2</sup> = 5	3%			+	
Test for overall effec	t: Z = 3.88 (P = 0.0001)	)			0.05	0.2 1	5	20
Test for subgroup dif	ferences: Chi <sup>2</sup> = 2.01	df = 1 (P = 0)	$(16)  ^2 =$	50.2%				

Figure 3. Forest plots for subgroup analyses of the association between tumor budding and OS of patients with BC. (A) Forest plots for subgroup analysis according to mean age of the patients; (B) Forest plots for subgroup analysis according to follow-up duration; (C) Forest plots for subgroup analysis according to analytic models. BC: Breast cancer; OS: Overall survival.

Δ					Hazard Ratio		Haza	ard Ratio	
<u>_</u>	Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI		IV, Ran	dom, 95%	CI
	Sun 2014	0.59222126	0.226831	14.6%	1.81 [1.16, 2.82]				
	Li 2017 ER+/HER2-	0.28517894	0.210706	15.1%	1.33 [0.88, 2.01]			+	
	Li 2017 TNBC	0	0.227289	14.6%	1.00 [0.64, 1.56]			+	
	Okcu 2021	0.76173997	0.371987	10.6%	2.14 [1.03, 4.44]				
	Xiang 2022	0.62593843	0.228987	14.6%	1.87 [1.19, 2.93]				
	Hiratsuka 2022	1.68639895	0.621658	6.0%	5.40 [1.60, 18.26]				
	Silva 2023	0.56531381	0.745169	4.6%	1.76 [0.41, 7.58]		_	· · ·	_
	Hou 2024	1.64074276	0.313411	12.2%	5.16 [2.79, 9.54]			•	
	Ozsen 2024	0.12221763	0.504938	7.8%	1.13 [0.42, 3.04]		_		
	Total (95% CI)			100.0%	1.89 [1.32, 2.71]			•	
	Heterogeneity: Tau <sup>2</sup> = 0	0.18; Chi <sup>2</sup> = 24.07, df	f = 8 (P = 0.	002); l <sup>2</sup> =	67%	0.05	0.2	1 5	20
	Test for overall effect: 2	Z = 3.46 (P = 0.0005)	)			0.05	0.2	1 5	20
					Harris Barla				
в	Other days and Outhermore	In all Incored Definit	05	W-1-64	Hazard Ratio		Haza	ard Ratio	<b>C</b> 1
-	Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI		IV, Ran	<u>dom, 95%</u>	CI
	2.2.1 Asian countries							_	
	Sun 2014	0.59222126	0.226831	14.6%	1.81 [1.16, 2.82]				
	Xiang 2022	0.62593843	0.228987	14.6%	1.87 [1.19, 2.93]				
	Hiratsuka 2022	1.68639895	0.621658	6.0%	5.40 [1.60, 18.26]				
	Hou 2024	1.64074276	0.313411	12.2%	5.16 [2.79, 9.54]				
	Subtotal (95% CI)			47.3%	2.77 [1.59, 4.84]				
	Heterogeneity: Tau <sup>2</sup> = 0	0.21; Chi <sup>2</sup> = 10.41, di	f = 3 (P = 0)	$(02); I^2 = 7$	1%				
	Test for overall effect: 2	Z = 3.59 (P = 0.0003)	)						
	0.0.0.11/								
	2.2.2 Western countri	es							
	Li 2017 ER+/HER2-	0.28517894	0.210706	15.1%	1.33 [0.88, 2.01]				
	Li 2017 TNBC	0	0.227289	14.6%	1.00 [0.64, 1.56]				
	Okcu 2021	0.76173997	0.371987	10.6%	2.14 [1.03, 4.44]		_		_
	Silva 2023	0.56531381	0.745169	4.6%	1.76 [0.41, 7.58]		_		
	Ozsen 2024	0.12221763	0.504938	7.8%	1.13 [0.42, 3.04]				
	Subtotal (95% CI)			52.7%	1.28 [0.98, 1.66]				
	Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>2</sup> = 3.37, df =	= 4 (P = 0.5	$(0); 1^2 = 0\%$	0				
	Test for overall effect: A	Z = 1.81 (P = 0.07)							
	T-1-1 (05% OI)								
				400 00/	4 00 14 00 0 741				
	Total (95% CI)			100.0%	1.89 [1.32, 2.71]			-	
	Heterogeneity: Tau <sup>2</sup> = 0	0.18; Chi² = 24.07, di	f = 8 (P = 0.	100.0% .002); l² =	1.89 [1.32, 2.71] 67%	0.05	0.2	1 5	20
	Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2	0.18; Chi <sup>2</sup> = 24.07, df Z = 3.46 (P = $0.0005$ )	f = 8 (P = 0. )	100.0% .002); l <sup>2</sup> =	1.89 [1.32, 2.71] 67%	0.05	0.2	1 5	20
	Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2 Test for suboroup differ	0.18; Chi² = 24.07, df Z = 3.46 (P = 0.0005) rences: Chi² = 6.08. d	f = 8 (P = 0. ) df = 1 (P = 0	100.0% .002); l <sup>2</sup> = 0.01). l <sup>2</sup> =	1.89 [1.32, 2.71] 67% 83.6%	0.05	0.2	1 5	20
6	Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for suboroup differ	0.18; Chi² = 24.07, df Z = 3.46 (P = 0.0005) rences: Chi² = 6.08. d	f = 8 (P = 0. ) df = 1 (P = (	100.0% .002); l <sup>2</sup> = 0.01). l <sup>2</sup> =	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio	0.05	0.2 Haza	1 5	20
С	Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subaroup differ Study or Subgroup	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08, d log[Hazard Ratio]	f = 8 (P = 0. ) df = 1 (P = 0 SE	100.0% 002); l <sup>2</sup> = 0.01). l <sup>2</sup> = Weight	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random, 95% CI	0.05	0.2 Haza	1 5 ard Ratio dom. 95%	20 CI
C	Hotal (95% C1) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subaroup differ Study or Subgroup 2.3.1 $\geq$ 5 buds/HPF	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio]	f = 8 (P = 0. ) df = 1 (P = ( SE	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = <u>Weight</u>	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio 	0.05	l 0.2 Haza IV. Ran	1 5 ard Ratio	20 CI
c	Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subaroup differ Study or Subgroup 2.3.1 $\geq$ 5 buds/HPF Sun 2014	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio] 0.59222126	f = 8 (P = 0. ) df = 1 (P = ( <u>SE</u> 0.226831	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = <u>Weight</u> 14.6%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio <u>IV. Random, 95% CI</u> 1.81 [1.16, 2.82]	0.05	l 0.2 Haza IV. Ran	ard Ratio	20 CI
c	Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subaroup differ Study or Subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2-	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio] 0.59222126 0.28517894	f = 8 (P = 0.) df = 1 (P = 0 <u>SE</u> 0.226831 0.210706	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = <u>Weight</u> 14.6% 15.1%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio <u>IV. Random, 95% CI</u> 1.81 [1.16, 2.82] 1.33 [0.88, 2.01]	0.05	0.2 Haza IV. Ran	ard Ratio	20 CI
C	Hotal (95% C1) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subaroup differ Study or Subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio] 0.59222126 0.28517890 0	f = 8 (P = 0.) df = 1 (P = 0 SE 0.226831 0.210706 0.227289	<b>100.0%</b> 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = <b>Weight</b> 14.6% 15.1% 14.6%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio <u>IV. Random, 95% CI</u> 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56]	0.05	0.2 Haza	ard Ratio	20 CI
c	Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect. 2 Test for subgroup differ Study or Subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 TNBC Silva 2023	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio] 0.59222126 0.28517894 0 0.565531381	f = 8 (P = 0.) df = 1 (P = 0 <u>SE</u> 0.226831 0.210706 0.227289 0.745169	<b>100.0%</b> 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = <b>Weight</b> 14.6% 15.1% 14.6% 4.6%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random. 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58]	0.05	l 0.2 Haza	ard Ratio	 20 CI
c	Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup differ Study or Subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio] 0.59222126 0.28517894 0 0.56531381 0.12221763	f = 8 (P = 0.) df = 1 (P = 0 <u>SE</u> 0.226831 0.210706 0.227289 0.745169 0.504938	<b>100.0%</b> 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = <b>Weight</b> 14.6% 15.1% 14.6% 4.6% 7.8%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio <u>IV, Random, 95% CI</u> 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.13 [0.42, 3.04]	0.05	0.2 Haza IV. Ran	ard Ratio dom. 95%	20 CI
c	Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI)	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio] 0.59222126 0.28517894 0 0.56531381 0.12221763	f = 8 (P = 0. ) df = 1 (P = 0 <u>SE</u> 0.226831 0.210706 0.227289 0.745169 0.504938	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = 14.6% 15.1% 14.6% 4.6% 7.8% 56.7%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random. 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.33 [0.42, 3.04] 1.34 [1.05, 1.70]	0.05	0.2 Haza IV. Ran	ard Ratio dom. 95%	<u> </u>
c	Hotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for suboroup differ Study or Subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = (	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio] 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00: Chi <sup>2</sup> = 3.65, df	f = 8 (P = 0.) df = 1 (P = 0 <u>SE</u> 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4	100.0% 002); l <sup>2</sup> = 0.01). l <sup>2</sup> = 14.6% 15.1% 14.6% 4.6% 7.8% 56.7% 6); l <sup>2</sup> = 09	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random, 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.13 [0.42, 3.04] 1.34 [1.05, 1.70]	0.05	0.2 Haza IV. Ran	ard Ratio dom. 95%	<u>    1                                </u>
c	Hotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for suboroup differ 2.3.1 $\geq$ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02)	f = 8 (P = 0.) df = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = 14.6% 15.1% 14.6% 4.6% 7.8% 56.7% 66); I <sup>2</sup> = 0%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random, 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.13 [0.42, 3.04] 1.34 [1.05, 1.70]	0.05	U.2 Hazı IV. Ran	ard Ratio dom. 95%	<u> </u>
C	Hotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subaroup differ 2.3.1 $\geq$ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08, d log[Hazard Ratio] 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02)	f = 8 (P = 0.) df = 1 (P = ( <u>SE</u> 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = <u>Weight</u> 14.6% 15.1% 14.6% 4.6% 7.8% 56.7% 6); I <sup>2</sup> = 0%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random, 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.13 [0.42, 3.04] 1.34 [1.05, 1.70]	0.05	I.2 Hazı IV. Ran	ard Ratio dom. 95%	<u> </u>
C	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 2.3.2 ≥ 7 or 8 buds/H	0.18; Chi <sup>2</sup> = 24.07, df Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02) PF	f = 8 (P = 0.) ff = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = <u>Weight</u> 14.6% 15.1% 14.6% 4.6% 7.8% 56.7% 6); I <sup>2</sup> = 0%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio <u>IV. Random, 95% CI</u> 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.13 [0.42, 3.04] 1.34 [1.05, 1.70]	0.05	U.2 Haza IV. Ran	ard Ratio dom. 95%	<u>-</u>
C	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 2.3.2 ≥ 7 or 8 buds/H Okcu 2021	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02) PF 0.76173997	f = 8 (P = 0.) ) ff = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4 0.371987	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = <u>Weight</u> 14.6% 15.1% 14.6% 4.6% 7.8% 56.7% 6); I <sup>2</sup> = 0% 10.6%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random. 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.33 [0.42, 3.04] 1.34 [1.05, 1.70] 2.14 [1.03, 4.44]	0.05	U.2 Hazı IV. Ran	ard Ratio dom. 95%	<u>-</u> 20
C	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 2.3.2 ≥ 7 or 8 buds/H Okcu 2021 Xiang 2022	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02) PF 0.76173997 0.62593843	f = 8 (P = 0.) f = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4 0.371987 0.228987	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = <u>Weight</u> 14.6% 15.1% 14.6% 4.6% 7.8% 56.7% 6); I <sup>2</sup> = 0% 10.6% 14.6%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random. 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.33 [0.42, 3.04] 1.34 [1.05, 1.70] 6 2.14 [1.03, 4.44] 1.87 [1.19, 2.93]	0.05	U.2 Haz: IV. Ran	ard Ratio dom. 95%	<u>-</u>
C	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subaroup differ 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 2.3.2 ≥ 7 or 8 buds/H Okcu 2021 Xiang 2022 Subtotal (95% CI)	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02) PF 0.76173997 0.62593843	f = 8 (P = 0.) df = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4 0.371987 0.228987	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = <u>Weight</u> 14.6% 14.6% 4.6% 7.8% 56.7% 66); I <sup>2</sup> = 0% 10.6% 14.6% 25.2%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random, 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.13 [0.42, 3.04] 1.34 [1.05, 1.70] 6 2.14 [1.03, 4.44] 1.87 [1.19, 2.93] 1.94 [1.32, 2.84]	0.05	U.2 Hazı IV. Ran	ard Ratio dom. 95%	<u>-</u> 20
C	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( 2.3.2 ≥ 7 or 8 buds/H Okcu 2021 Xiang 2022 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = (	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02) PF 0.76173997 0.62593843	f = 8 (P = 0.) df = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4 0.371987 0.228987 = 1 (P = 0.7	100.0% 002);   <sup>2</sup> = 0.01).   <sup>2</sup> = 14.6% 15.1% 14.6% 4.6% 7.8% 56.7% 6);   <sup>2</sup> = 0% 10.6% 14.6% 25.2% 6);   <sup>2</sup> = 0%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random, 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.13 [0.42, 3.04] 1.34 [1.05, 1.70] 6 2.14 [1.03, 4.44] 1.87 [1.19, 2.93] 1.94 [1.32, 2.84]	0.05	I Haza	ard Ratio dom. 95%	<u>-</u> 20
C_	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( 2.3.2 ≥ 7 or 8 buds/H Okcu 2021 Xiang 2022 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Subtotal (95% CI)	0.18; Chi <sup>2</sup> = 24.07, df Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08, d 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02) PF 0.76173997 0.62593843 0.00; Chi <sup>2</sup> = 0.10, df Z = 3.40 (P = 0.007)	f = 8 (P = 0. ) df = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4 0.371987 0.228987 = 1 (P = 0.7	100.0% 002);   <sup>2</sup> = 0.01).   <sup>2</sup> = 14.6% 15.1% 14.6% 4.6% 7.8% 56.7% 6);   <sup>2</sup> = 0% 10.6% 14.6% 25.2% (6);   <sup>2</sup> = 0%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random, 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.13 [0.42, 3.04] 1.34 [1.05, 1.70] 6 2.14 [1.03, 4.44] 1.87 [1.19, 2.93] 1.94 [1.32, 2.84]	0.05	IV. Ran	ard Ratio dom. 95%	<u>cı</u>
C _	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Ckcu 2021 Xiang 2022 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Subtotal (95% CI) Subtotal (95% CI)	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio] 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02) PF 0.76173997 0.62593843 0.00; Chi <sup>2</sup> = 0.10, df Z = 3.40 (P = 0.0007)	f = 8 (P = 0.) ff = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4 0.371987 0.228987 = 1 (P = 0.7)	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = 14.6% 15.1% 14.6% 14.6% 56.7% 6); I <sup>2</sup> = 0% 10.6% 14.6% 25.2% (6); I <sup>2</sup> = 0%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random, 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.13 [0.42, 3.04] 1.34 [1.05, 1.70] 6 2.14 [1.03, 4.44] 1.87 [1.19, 2.93] 1.94 [1.32, 2.84]	0.05	U.2 Haz: <u>IV. Ran</u>	ard Ratio dom. 95%	<u>-</u>
C	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( 2.3.2 ≥ 7 or 8 buds/H Okcu 2021 Xiang 2022 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 2.3.3 ≥ 10 buds/HPF	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio] 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02) PF 0.76173997 0.62593843 0.00; Chi <sup>2</sup> = 0.10, df Z = 3.40 (P = 0.0007)	f = 8 (P = 0.) ) ff = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4 0.371987 0.228987 = 1 (P = 0.7)	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = 14.6% 15.1% 14.6% 14.6% 56.7% 6); I <sup>2</sup> = 0% 10.6% 14.6% 25.2% 6); I <sup>2</sup> = 0%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random. 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.33 [0.42, 3.04] 1.34 [1.05, 1.70] 6 2.14 [1.03, 4.44] 1.87 [1.19, 2.93] 1.94 [1.32, 2.84]	0.05	U.2 Hazı IV. Ran	ard Ratio dom. 95%	<u>-</u> 20
C_	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( 2.3.2 ≥ 7 or 8 buds/H Okcu 2021 Xiang 2022 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 2.3.3 ≥ 10 buds/HPF Hiratsuka 2022	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio] 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02) PF 0.76173997 0.62593843 0.00; Chi <sup>2</sup> = 0.10, df Z = 3.40 (P = 0.0007) 1.68639895	f = 8 (P = 0. ) ff = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4 0.371987 0.228987 = 1 (P = 0.7) 0.621658	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = 14.6% 15.1% 14.6% 14.6% 7.8% 56.7% 6); I <sup>2</sup> = 0% 10.6% 14.6% 25.2% 6); I <sup>2</sup> = 0% 6.0%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random, 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.13 [0.42, 3.04] 1.34 [1.05, 1.70] 6 2.14 [1.03, 4.44] 1.87 [1.19, 2.93] 1.94 [1.32, 2.84] 6	0.05	U.2 Haz: IV. Ran	ard Ratio dom. 95%	<u> </u>
c	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( 2.3.2 ≥ 7 or 8 buds/H Okcu 2021 Xiang 2022 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 2.3.3 ≥ 10 buds/HPF Hiratsuka 2022 Hou 2024	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio] 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02) PF 0.76173997 0.62593843 0.00; Chi <sup>2</sup> = 0.10, df Z = 3.40 (P = 0.0007) 1.68639895 1.64074276	f = 8 (P = 0.) f = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4 0.371987 0.228987 = 1 (P = 0.7) 0.621658 0.313411	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = 14.6% 15.1% 14.6% 4.6% 7.8% 56.7% 6); I <sup>2</sup> = 0% 10.6% 14.6% 25.2% 6); I <sup>2</sup> = 0% 6.0% 12.2%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random, 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.13 [0.42, 3.04] 1.34 [1.05, 1.70] 6 2.14 [1.03, 4.44] 1.87 [1.19, 2.93] 1.94 [1.32, 2.84] 5.40 [1.60, 18.26] 5.16 [2.79, 9.54]	0.05	U.2 Hazı IV. Ran	ard Ratio dom. 95%	<u>cı</u>
C	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( 2.3.2 ≥ 7 or 8 buds/H Okcu 2021 Xiang 2022 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( 1.3.2 ≥ 7 or 8 buds/H Okcu 2021 Xiang 2022 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( 1.3.3 ≥ 10 buds/HPF Hiratsuka 2022 Hou 2024 Subtotal (95% CI)	0.18; Chi <sup>2</sup> = 24.07, df Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08, d 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02) PF 0.76173997 0.62593843 0.00; Chi <sup>2</sup> = 0.10, df Z = 3.40 (P = 0.0007) 1.68639895 1.64074276	f = 8 (P = 0.) df = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4 0.371987 0.228987 = 1 (P = 0.7) 0.621658 0.313411	100.0% 002);   <sup>2</sup> = 0.01).   <sup>2</sup> = 14.6% 15.1% 14.6% 4.6% 7.8% 56.7% 6);   <sup>2</sup> = 0% 10.6% 14.6% 25.2% (6);   <sup>2</sup> = 0% 6.0% 12.2% 18.1%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random, 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.13 [0.42, 3.04] 1.34 [1.05, 1.70] 6 2.14 [1.03, 4.44] 1.37 [1.19, 2.93] 1.94 [1.32, 2.84] 5.40 [1.60, 18.26] 5.16 [2.79, 9.54] 5.21 [3.01, 9.01]	0.05	U.2 Hazı IV. Ran	ard Ratio dom. 95%	
C	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 2.3.2 ≥ 7 or 8 buds/HP Okcu 2021 Xiang 2022 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( 2.3.3 ≥ 10 buds/HPF Hiratsuka 2022 Hou 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( 2.3.3 ≥ 10 buds/HPF Hiratsuka 2022 Hou 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = (	0.18; Chi <sup>2</sup> = 24.07, df Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio] 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02) PF 0.76173997 0.62593843 0.00; Chi <sup>2</sup> = 0.10, df Z = 3.40 (P = 0.0007) 1.68639895 1.64074276 0.00; Chi <sup>2</sup> = 0.00, df	f = 8 (P = 0.) f = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4 0.371987 0.228987 = 1 (P = 0.7 0.621658 0.313411 = 1 (P = 0.9	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = 14.6% 15.1% 14.6% 14.6% 56.7% 6); I <sup>2</sup> = 0% 10.6% 14.6% 25.2% 6); I <sup>2</sup> = 0% 10.6% 14.6% 25.2% 10.6% 14.6% 14.6% 25.2% 10.6% 14.6% 14.6% 14.6% 14.6% 15.1% 14.6%	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random, 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.13 [0.42, 3.04] 1.34 [1.05, 1.70] 6 2.14 [1.03, 4.44] 1.87 [1.19, 2.93] 1.94 [1.32, 2.84] 6 5.40 [1.60, 18.26] 5.16 [2.79, 9.54] 5.21 [3.01, 9.01]	0.05	U.2 Haz: <u>IV. Ran</u>	ard Ratio dom. 95%	CI
C	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Test for subgroup 2.3.1 ≥ 5 buds/HPF Sun 2014 Li 2017 ER+/HER2- Li 2017 TNBC Silva 2023 Ozsen 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 2.3.2 ≥ 7 or 8 buds/H Okcu 2021 Xiang 2022 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 2.3.3 ≥ 10 buds/HPF Hiratsuka 2022 Hou 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( 1.3.3 ≥ 10 buds/HPF Hiratsuka 2022 Hou 2024 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Subtotal (95% CI)	0.18; Chi <sup>2</sup> = 24.07, dt Z = 3.46 (P = 0.0005) rences: Chi <sup>2</sup> = 6.08. d log[Hazard Ratio] 0.59222126 0.28517894 0 0.56531381 0.12221763 0.00; Chi <sup>2</sup> = 3.65, df Z = 2.37 (P = 0.02) PF 0.76173997 0.62593843 0.00; Chi <sup>2</sup> = 0.10, df Z = 3.40 (P = 0.0007) 1.68639895 1.64074276 0.00; Chi <sup>2</sup> = 0.00, df Z = 5.90 (P < 0.0000)	f = 8 (P = 0.) f = 1 (P = ( 0.226831 0.210706 0.227289 0.745169 0.504938 = 4 (P = 0.4 0.371987 0.228987 = 1 (P = 0.7) 0.621658 0.313411 = 1 (P = 0.9 1)	100.0% 002); I <sup>2</sup> = 0.01). I <sup>2</sup> = 14.6% 15.1% 14.6% 14.6% 56.7% 6); I <sup>2</sup> = 0% 10.6% 14.6% 25.2% (6); I <sup>2</sup> = 0% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 14.6% 25.2% 10.6% 12.2% 18.1% 18.1% 18.1% 19.2% 18.1% 19.2% 19.2% 19.2% 19.2% 10.6% 19.2% 10.6% 19.2% 10.6% 10.5% 10.6% 10.6% 10.6% 10.6% 10.6% 10.6% 10.6% 10.6% 10.6% 10.6% 10.6% 10.6% 10.6% 10.6% 10.6% 10.6% 10.6% 10.6% 10.5% 10.6	1.89 [1.32, 2.71] 67% 83.6% Hazard Ratio IV. Random. 95% CI 1.81 [1.16, 2.82] 1.33 [0.88, 2.01] 1.00 [0.64, 1.56] 1.76 [0.41, 7.58] 1.33 [0.42, 3.04] 1.34 [1.05, 1.70] 6 2.14 [1.03, 4.44] 1.87 [1.19, 2.93] 1.94 [1.32, 2.84] 6 5.40 [1.60, 18.26] 5.16 [2.79, 9.54] 5.21 [3.01, 9.01] 6	0.05	U.2 Hazı IV. Ran	ard Ratio dom. 95%	CI
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Figure 6. Funnel plots for the meta-analysis of the associations of tumor budding with OS and PFS in patients with BC. (A) Funnel plots for the outcome of OS; (B) Funnel plots for the outcome of PFS. BC: Breast cancer; OS: Overall survival; PFS: Progression-free survival.

and Notch are known to play crucial roles in EMT and tumor budding [38]. These pathways facilitate the detachment of tumor cells from the primary mass, enhancing their invasive potential and contributing to metastasis and therapy resistance [39, 40]. Consequently, the presence of tumor budding reflects a more aggressive tumor phenotype, which could lead to poorer survival outcomes in BC patients. The subgroup analyses provided further insights into the impact of tumor budding on survival outcomes. Interestingly, the cutoff used to define high tumor budding significantly influenced the strength of the association with OS and PFS, which fully explained the source of statistical heterogeneity. Studies that used a cutoff of > 10 buds/HPF reported a much stronger association between high tumor budding and poor survival compared to studies with lower cutoffs. This variation might be due to differences in the sensitivity and specificity of detecting truly aggressive tumor cells. A higher cutoff could better capture the most aggressive and clinically relevant tumor budding, leading to a more pronounced impact on survival outcomes. Conversely, lower cutoffs might include less aggressive tumor cells, diluting the association with poor prognosis. Similarly, a study in colorectal cancer patients demonstrated that tumor budding with  $\geq$ 10 tumor buds/HPF was associated with a more than twofold

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increased risk of cancer-specific death, whereas the association was not significant for patients with 1–9 tumor buds/HPF [41]. These findings underscore the importance of standardizing criteria for defining and assessing tumor budding to ensure consistency and comparability across studies. It is also important to consider the influence of study quality (as measured by NOS) on the outcomes of this meta-analysis. According to the NOS criteria, a score of 7–9 indicates good study quality [42]. The NOS scores of the included studies ranged from 6 to 9. Notably, studies with a score of 6 (indicating moderate quality) primarily used univariate analysis, while studies with scores of 7–9 (indicating high quality) utilized multivariate analysis. Our subgroup analysis revealed similar outcomes between univariate and multivariate analyses, further demonstrating consistent results across studies of both moderate and high quality.

#### Limitations

The current meta-analysis has several strengths. First, it adhered to rigorous methodological standards, including a comprehensive literature search, well-defined inclusion criteria, and robust statistical analyses. The inclusion of studies from diverse geographic regions enhances the generalizability of the findings. Second, the meta-analysis only included cohort studies, which offer a longitudinal relationship between tumor budding and poor survival outcomes in BC patients [43]. Additionally, we performed multiple sensitivity and subgroup analyses to confirm the robustness of the findings and explore sources of heterogeneity. Specifically, positive results in subgroup analyses limited to multivariate studies suggest that the association between tumor budding and poor survival may be independent of potential confounding factors, such as age, tumor grade, or tumor stage, providing more reliable estimates of this relationship.

However, several limitations should be acknowledged. All included studies were retrospective cohort studies, which are subject to inherent biases such as selection bias and recall bias [44]. The heterogeneity in the methodologies used to assess tumor budding-including differences in staining techniques and cutoffs for defining high tumor buddingmight have contributed to variability in the results. Despite using a random-effects model to account for between-study heterogeneity [45], the presence of significant heterogeneity in some subgroup analyses indicates that other unmeasured factors might influence the association between tumor budding and survival outcomes. Furthermore, as this is a meta-analysis of observational studies, the causation between high tumor budding and poor survival in BC cannot be definitively established based on the current results. Lastly, the potential influence of hormone receptor status [46] and BC subtypes [47] on the meta-analysis outcome could not be determined because stratified data by these factors were not commonly reported in the included studies. Further investigation is warranted in future studies.

#### **Clinical implications**

From a clinical perspective, the findings of this meta-analysis emphasize the potential of tumor budding as a prognostic

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marker in BC. Identifying patients with high tumor budding could help stratify risk and guide treatment decisions. For instance, patients with high tumor budding might benefit from more aggressive therapeutic strategies and closer surveillance to improve their outcomes. Additionally, the results highlight the need for further research to validate the prognostic value of tumor budding in larger, prospective studies and to standardize tumor budding assessments in clinical practice. Future research should also explore the molecular mechanisms underlying the association between tumor budding and poor survival in BC. Investigating the role of EMT and related pathways in tumor budding could provide valuable insights into the biology of tumor progression and metastasis [48]. Moreover, it is crucial to assess whether integrating tumor budding assessment with other established prognostic markers, such as hormone receptor status and HER2 expression, could enhance the accuracy of risk stratification and personalized treatment approaches [49].

# Conclusion

In conclusion, this meta-analysis demonstrates that high tumor budding is significantly associated with poorer OS and PFS in patients with BC. The impact of the cutoff for defining high tumor budding on survival outcomes underscores the need for standardized assessment criteria. Future research should aim to validate these findings in larger, prospective studies and further elucidate the underlying molecular mechanisms to improve the management and outcomes of BC patients.

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Conflicts of interest: Authors declare no conflicts of interest.

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**Data availability:** All the data generated during the study was within the manuscript.

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# Supplemental data

#### Supplemental File 1. Detailed search strategy

#### PubMed (n = 46)

(("budding" [All Fields] OR "sprouting" [All Fields] OR "bud" [All Fields] OR "buds" [All Fields] OR "tumor cell dissociation" [All Fields]) AND ("breast neoplasms" [MeSH Terms] OR "breast cancer" [All Fields]) AND ("mortality" [MeSH Terms] OR "survival" [MeSH Terms] OR "recurrence" [MeSH Terms] OR "death" [MeSH Terms] OR "prognosis" [MeSH Terms] OR "progression" [MeSH Terms] OR "metastasis" [MeSH Terms]))

#### Embase (n = 91)

('budding' OR 'sprouting' OR 'bud' OR 'buds' OR 'tumor cell dissociation') AND ('breast cancer'/exp OR 'breast cancer') AND ('mortality'/exp OR 'survival'/exp OR 'recurrence'/exp OR 'death'/exp OR 'prognosis'/exp OR 'progression'/exp OR 'metastasis'/exp) AND [humans]/lim AND [clinical study]/lim AND [embase]/lim

#### Web of Science (n = 427)

TS = (("budding" OR "sprouting" OR "bud" OR "buds" OR "tumor cell dissociation") AND ("breast cancer") AND ("mortality" OR "survival" OR "recurrence" OR "death" OR "prognosis" OR "progression" OR "metastasis"))