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META-ANALYSIS

Predictive value of tumor-infiltrating lymphocytes for neoadjuvant therapy response in triple-negative breast cancer: A systematic review and meta-analysis

Hai-Kuan Sun, Wen-Long Jiang, Shi-Lei Zhang, Peng-Cheng Xu, Li-Min Wei, Jiang-Bo Liu

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Hai-Kuan Sun, Wen-Long Jiang, Shi-Lei Zhang, Peng-Cheng Xu, Li-Min Wei, Jiang-Bo Liu, Department of Thyroid and Breast Surgery, The First Affiliated Hospital, College of Clinical Medicine, Henan University of Science and Technology, Luoyang 471000, Henan Province, China

Co-first authors: Hai-Kuan Sun and Wen-Long Jiang.

Corresponding author: Jiang-Bo Liu, Doctor, PhD, Associate Professor, Department of Thyroid and Breast Surgery, The First Affiliated Hospital, College of Clinical Medicine, Henan University of Science and Technology, No. 24 Jinghua Road, Luoyang 471000, Henan Province, China. jiangboliuxing@163.com

Abstract

BACKGROUND

The association between tumor-infiltrating lymphocyte (TIL) levels and the response to neoadjuvant therapy (NAT) in patients with triple-negative breast cancer (TNBC) remains unclear.

AIM

To investigate the predictive potential of TIL levels for the response to NAT in TNBC patients.

METHODS

A systematic search of the National Center for Biotechnology Information PubMed database was performed to collect relevant published literature prior to August 31, 2023. The correlation between TIL levels and the NAT pathologic complete response (pCR) in TNBC patients was assessed using a systematic review and meta-analysis. Subgroup analysis, sensitivity analysis, and publication bias analysis were also conducted.

RESULTS

A total of 32 studies were included in this meta-analysis. The overall meta-analysis results indicated that the pCR rate after NAT treatment in TNBC patients in the high TIL subgroup was significantly greater than that in patients in the low TIL subgroup (48.0% *vs* 27.7%) (risk ratio 2.01; 95% confidence interval 1.77-2.29; $P < 0.001$, $I^2 = 56\%$). Subgroup analysis revealed that the between-study heterogeneity originated from differences in study design, TIL level cutoffs, and study

populations. Publication bias could have existed in the included studies. The meta-analysis based on different NAT protocols revealed that all TNBC patients with high levels of TILs had a greater rate of pCR after NAT treatment in all protocols (all $P \leq 0.01$), and there was no significant between-protocol difference in the statistics among the different NAT protocols ($P = 0.29$). Additionally, sensitivity analysis demonstrated that the overall results of the meta-analysis remained consistent when the included studies were individually excluded.

CONCLUSION

TILs can serve as a predictor of the response to NAT treatment in TNBC patients. TNBC patients with high levels of TILs exhibit a greater NAT pCR rate than those with low levels of TILs, and this predictive capability is consistent across different NAT regimens.

Key Words: Breast cancer; Tumor-infiltrating lymphocyte; Neoadjuvant therapy; Treatment response; Systematic review; Meta-analysis

Core Tip: The immune response status may have a significant impact on the effectiveness of chemotherapy. Tumor-infiltrating lymphocytes (TILs) can directly or indirectly participate in specific immune responses against tumor cells. However, the association between TIL levels and the response to neoadjuvant therapy (NAT) in patients with triple-negative breast cancer (TNBC) remains unclear. This systematic review and meta-analysis first investigated the relationship between TIL status and the response to NAT in TNBC patients. This systematic review and meta-analysis will provide clinical physicians with systematic evidence on the role of TILs to predict the response of TNBC patients to NAT.

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INTRODUCTION

Global Cancer Statistics 2020 reported that in 2020, breast cancer (BC) was becoming the most common malignant tumor globally[1]. Triple-negative BC (TNBC) is characterized by extremely aggressive biological behavior and has a high recurrence rate and poor survival[2,3]. Extensive investigations on early diagnosis, precision treatment, and prognostic prediction have been conducted to improve TNBC patient survival[4-6]. Neoadjuvant therapy (NAT) can effectively decrease the clinical stage of TNBC, and patients who attain pathologic complete response (pCR) following NAT have significantly prolonged event-free survival (EFS) and overall survival compared with those having residual infiltrative carcinoma. Consequently, NAT has been widely recommended as the preferred preoperative standard treatment modality for TNBC patients with lymph node involvement and/or stage ≥ T1c disease[7,8].

The immune response status may have a significant impact on the effectiveness of chemotherapy[9,10]. Research findings indicate that in early-stage TNBC patients, the NAT protocol combining the immune checkpoint inhibitor pembrolizumab, which enhances the functionality of activated T cells, with conventional chemotherapy drugs has been correlated with increased rates of pCR and prolonged EFS[11,12]. Tumor-infiltrating lymphocytes (TILs) can directly or indirectly participate in specific immune responses against tumor cells, and their aggregation, interaction, and costimulation are essential for successful antitumor immune responses[13,14]. High levels of TILs within the tumor or the stroma are associated with a more favorable response to NAT in early-stage and locally advanced TNBC patients[15-19]. However, this result was not substantiated in a study that conducted a meta-analysis of individual patient data from a phase II study of TNBC NATs involving five different platinum-based regimens[20]. Therefore, further investigations are warranted to explore the correlation between TIL levels and therapeutic response in TNBC NATs.

Previously, a systematic review and meta-analysis on the correlation between TIL levels in different molecular subtypes of BC and NAT response showed that high levels of TILs are associated with pCR in a TNBC subgroup analysis including four studies[21]. Over the past decade, many clinical trials have further investigated the effectiveness of different NAT regimens for TNBC and employed TIL levels to predict treatment response and long-term prognosis. Consequently, this study was designed to analyze the ability of TILs in TNBC patients to predict the response to NAT through a more comprehensive systematic review and meta-analysis, with the objective of obtaining more current and robust research evidence. Additionally, this study examined the predictive importance of TIL levels for the therapeutic efficacy of different NAT regimens in TNBC patients.

MATERIALS AND METHODS

The present meta-analysis adhered to the reporting suggestions provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[22].

Literature search and inclusion criteria

The literature search was conducted on the National Center for Biotechnology Information PubMed (MEDLINE) database to identify pertinent articles published prior to August 31, 2023. The search strategy involved utilizing a combination of the following MeSH terms, title/abstract keywords, or full-text search terms: "breast cancer, or breast carcinoma" , "triple-negative, or TNBC" , "neoadjuvant therapy, or neoadjuvant" , and "tumor-infiltrating lymphocytes, T lymphocytes, or TILs" . Additionally, a manual search of the literature and reference tracing were performed to identify any additional relevant studies.

The studies eligible for this meta-analysis met the following criteria: (1) Pathological and immunohistochemical-based molecular subtyping confirming the diagnosis of TNBC; (2) Reported TIL levels by hematoxylin and eosin staining evaluation according to the standardized method presented by the International TILs Working Group in 2014 or other explicit assays; (3) Reported the number or rate of pCR events in TNBC patients based on different TIL levels; and (4) Were published in either English or Chinese.

Three researchers (Sun HK, Jiang WL, and Zhang SL) independently evaluated the titles and abstracts of the candidate studies, excluding those not pertinent to the topic. Subsequently, both researchers thoroughly examined the full texts to determine their eligibility for inclusion. In cases where uncertainty arose or disagreements occurred regarding inclusion, the researchers resorted to the study designer (Liu JB) for a review and discussion to achieve consensus. Furthermore, if multiple publications involved the same study population, priority was given to the publication with a larger sample size or the most recent study for eligibility in the meta-analysis.

Data extraction and quality assessment

Three researchers (Sun HK, Jiang WL, and Zhang SL) independently collected the relevant information and data for each study that met the inclusion criteria using a predesigned table. These included details such as the first author, geographical location of the study population, publication year, study design, recruitment year, TNM staging, NAT regimen, number of high/low TILs, cutoff values and methodology used, treatment response endpoints and pCR criteria as well as the number and ratio of pCR events. Next, the quality of the cohort studies included was independently assessed by two researchers (Sun HK and Jiang WL) using the Newcastle-Ottawa Scale (NOS)[23].

Statistical analysis

The meta-analysis was conducted in RevMan 5.4 software. The total cases of patients and the cases of patients who achieved pCR were recorded separately for the high TIL level group and low TIL level group in each study and input into RevMan software. The relative risk ratio (RR) and the associated 95% confidence interval (CI) were calculated per the following formula: The pCR rate in the high TIL level group divided by the pCR rate in the low TIL level group. RR > 1 and $P < 0.05$ indicated a greater pCR rate in the high TIL level subgroup than in the low TIL level subgroup.

In the meta-analysis, between-study heterogeneity was assessed using the I^2 statistic (ranging from 0% to 100%). If an I^2 value less than 50% or a P value greater than 0.05 indicated the absence or low between-study heterogeneity, a fixed-effects model was used for meta-analysis; otherwise, a random-effects model (REM) was used. Additionally, subgroup analysis was conducted to explore the source of between-study heterogeneity when significant heterogeneity was observed, and sensitivity analysis was performed to evaluate the influence of individual studies on the overall meta-analysis results. Publication bias was investigated using a funnel plot and Egger's test. If funnel plot is asymmetric or a P value is less than 0.05 according to Egger's test, publication bias was considered present[24]. Duval and Tweedie trim-and-fill method was used for testing and adjusting for publication bias in meta-analysis[25]. All the statistical tests were two-tailed, and $P < 0.05$ was considered indicative of statistical significance.

RESULTS

Study selection

A preliminary literature search identified 269 articles, and after reviewing the titles and abstracts, we selected 158 articles for full-text reading. Subsequently, 125 articles were excluded because of the eligibility criteria. Finally, 32 eligible studies comprising 5406 TNBC patients were included in this systematic review and meta-analysis. The NOS quality scores of the eligible studies ranged from 6 to 9, with a median score of 8 (Figure 1).

Characteristics of the included studies

Table 1 displays the characteristics of all the studies included in the analysis. Among the 32 included studies, 16 studies provided descriptions of TNBC before NAT based on T staging, including 4051 cases in T1/T2, 48 cases in T2/T3, 341 cases in T2-T4, and 1007 cases in T3/T4; fifteen (15) studies described N staging of pre-NAT TNBC, including 2937 cases in N0 and 2,704 cases in N1-N3; additionally, 11 studies described the clinical TNM staging of pre-NAT TNBC, including 91 cases in stage I, 923 cases in stage II, and 762 cases in stage III; and five studies did not report T or N stage or clinical TNM staging. Among the 27 included studies, TIL levels were assessed per the standardized method proposed by the

Table 1 Characteristics of the impact of tumor-infiltrating lymphocytes on the response to neoadjuvant therapy in triple-negative breast cancer patients included in the meta-analysis

Ref.	Data collection	Recruitment period	Sample size	Age in yr, median/mean (range)	TNM stage	Neoadjuvant regimen	Number of high/middle TILs as %, cut-off, and method	End point and pCR standard	Number of overall pCR as %	pCR rates as high TILs *vs* low TILs	OR or RR
Cerbelli *et al*[36], Germany	Retrospective consecutive cohort	2011.6-2017.6	61	50 (28-74)	T1: 8; T2: 46; T3: 3; T4: 4; N0: 32; N1-N3: 29	AC×4 (Q3W) →T×12 (QW)	49 (17/32) (80.3), (50%) 10%, HE	pCR, ypT0	23 (37.7)	18 (36.7) *vs* 5 (41.7)	OR: [U] 0.41 (0.17-0.95), 0.037; [M] 2.39 (0.96-5.96), 0.062
Galvez *et al*[17], Peru	Retrospective cohort	2003.1-2014.12	435	49 (24-84)	II: 72, III: 363;	AC×4 (Q3W) →T×12 (QW)	181 (41.6), 50%, HE	pCR, ypT0	46 (11.0)	26 (14.4) *vs* 20 (7.9)	NR
Abdelrahman *et al*[39], Egypt	Prospective cohort	2017.1-2019.5	50	45 (22-72)	T1: 20; T2: 30; N0: 18; N1-N3: 32	AC→T	14 (28.0), 50%, HE	pCR, ypT0	20 (40.0)	10 (71.4) *vs* 10 (27.8)	NR
Jung *et al*[53], Korea	Retrospective cohort	2009.1-2014.12	143	NR	T1-T2: 91; T3: 52; N0: 64; N1-N3: 79	AC→T	74 (51.7), 30%, HE	pCR, ypT0	66 (46.2)	43 (58.1) *vs* 23 (33.3)	OR: [U] 2.774 (1.404-5.481), 0.003; [M] 3.484 (1.407-8.627), 0.007
Russo *et al*[47], Venezuela	Retrospective cohort	2008-2013	41	NR	II: 80, III: 107;	AC→T	14 (34.1), 30%, HE	pCR, ypT0	15 (36.6)	11 (78.6) *vs* 4 (14.8)	OR: [U] 8.85 (3.62-21.66), 0.001
Vicent *et al*[48], Spain	Retrospective cohort	1998-2015	164	49 (29-81)	II: 63, III: 37	AC×4 (Q3W) →T×12 (QW)	58 (35.4), 40%, HE	pCR, ypT0/is, ypN0	61 (37.2)	51 (88.0) *vs* 10 (9.0)	NR
Ochi *et al*[32], Japan	Retrospective consecutive cohort	2001-2009	80	52 (27-75)	NR	AC→T	55 (19/36) (68.8), (50%) 10%, HE	pCR, ypT0	25 (31.3)	24 (43.6) *vs* 1 (4.0)	NR
Bockstal *et al*[49], Belgium	Retrospective consecutive cohort	2015.1-2020.3	35	55.8 ± 13.3	NR	AC→T	10 (28.6), 40%, HE	pCR, ypT0	13 (37.1)	8 (80.0) *vs* 5 (20.0)	NR
Rangan *et al*[43], India	NR	NR	75	NR	T1-T3: 49; T4: 26; N0: 36; N1-N3: 39	NR	57 (76.0), 50%, HE	pCR, ypT0	27 (36.0)	25 (43.9) *vs* 2 (11.1)	OR: [U] 6.25 (1.312-29.763), 0.025
Pang *et al*[18], ChiNR	Retrospective cohort	2010.1-2018.12	310	NR	T1-2: 298; T3-4: 97	AC→T	177 (85/92) (57.1), (20%) 10%, HE	pCR, ypT0	88 (28.4)	53 (31.1) *vs* 33 (34.5)	NR
Zhang *et al*[52], America	Retrospective cohort	2005-2016	58	46 (24-64)	T1: 7; T2-T4: 51; N0: 30; N1-N3: 28	AC×4 (Q3W) →T×12 (QW)	17 (29.3), 60%, HE	pCR, ypT0	26 (44.8)	12 (70.6) *vs* 14 (34.1)	NR
Zhao *et al*[50], ChiNR	Retrospective cohort	2017-2018	126	50.1 ± 11.2	T1: 78; T2-T3: 48; N0: 74; N1-N3: 52	AC→T	42 (33.3), 40%, HE	pCR, ypT0	76 (60.3)	38 (90.5) *vs* 38 (45.2)	NR
Cerbelli *et al*[40],	Retrospective	2011.1-2016.12	54	50 (28-75)	T1: 7; T2-T4:	AC×4 (Q3W) →T×12	22 (40.7), 50%, HE	pCR, ypT0/is,	19 (35.2)	11 (50.0) *vs* 8	OR: [U] 1.61 (0.40-6.52),

Italy	consecutive cohort				47; N0: 24; N1-N3: 30	(QW)		N0		(25.0)	0.025
Rao *et al*[30], ChiNR	Retrospective consecutive cohort	2009.7-2014.6	52	46.9 (23-67)	II: 34, III: 16;	TAC	21 (40.4), CD8: ≥ 0.15, HE	pCR, ypT0 DFS OS	14 (26.9)	CD8: 10 (47.6) *vs* 4 (12.9)	CD8 OR: [U] 6.14 (1.6-23.8), 0.010
Lusho *et al*[28], Japan	Retrospective consecutive cohort	2008-2019	120	56 (28-86)	NR	TAC	18 (15.0), 30%, HE	pCR, ypT0/Tis ypN0	34 (28.3)	10 (55.6) *vs* 24 (23.5)	NR
Hida *et al*[37], Japan	Retrospective cohort	2007-2014	48	56 (22-79)	T1: 93; T2: 59; T3: 2; N0: 98; N1-N3: 56	AC×4 (Q3W) →T×12 (QW)	31 (11/20) (64.6), (50%) 10%, HE	pCR, ypT0/is, ypN0	21 (43.8)	18 (58.0) *vs* 3 (17.6)	NR
Hida *et al*[27], Japan	Retrospective consecutive cohort	2007-2014	80	NR	N0: 56; N1-N3: 24	TAC	23 (28.8), 50%, HE	pCR, ypT0/is, N0	28 (35.0)	12 (52.2) *vs* 16 (28.1)	NR
Kolberg *et al*[51], Germany	Retrospective cohort	NR	311	NR	NR	AC→T	59 (19.0), 60%, HE	pCR, ypT0	110 (35.4)	35 (59.3) *vs* 75 (29.8)	OR: [U] 3.44 (1.92-6.18), 0.001
Foldi *et al*[38], America	II RCT	2015.12-2018.11	54	NR	I: 12, II: 33, III: 14;	T→ddAC- Durvalumab (3 and 10 mg/kg)	26 (16/10) (48.1), (30%) 10%, HE	pCR, ypT0/Tis ypN0	23 (42.6)	15 (57.7) *vs* 8 (28.6)	NR
Abuhadra *et al* [16], America	Prospective cohort	2015.10-2019.11	318	52.5 (24-77)	I: 38, II: 210, III: 70;	ddAC→T+ (Atezolizumab/ Panitumumab/ Bevacizumab)	106 (33.3), 20%, HE	pCR, ypT0	130 (40.9)	68 (64.2) *vs* 62 (29.2)	NR
Denkert *et al* [33], Germany	RCT IPD pooled analysis	2010.1-2016.12	906	NR	NR	T+ Bevacizumab	646 (273/373) (71.3), (60%) 10%, HE	pCR, ypT0	333 (36.8)	253 (39.2) *vs* 80 (30.8)	NR
Yuan *et al*[34], America	II RCT	2012.1-2018.8	63	52 (28-79)	II: 55, III: 12;	TCb	28 (6/22) (45.9), (60%) 10%, HE	pCR, ypT0	30 (47.6)	17 (60.7) *vs* 13 (39.3)	Medium *vs* low[1]: OR: [U] 2.23 (0.74- 6.69), 0.16; high *vs* low[1]: OR: [U] 3.06 (0.49-9.30), 0.23
Sharma *et al*[46], America	II RCT	2015.7-2018.5	100	51 (29–70)	T1: 19; T2: 70; T3-T4: 11; N0: 70; N1-N3: 30	Arm-A: CbP + AC; Arm-B: CbD	39 (43.3), 20%, HE	pCR ypT0/is, ypN0	51 (56.7)	26 (66.7) *vs* 25 (49.0)	OR: [U] 2.08 (0.88-4.93), 0.096
Pons *et al*[45], Spain	NR	2016-2022	67	NR	T1-T2: 59; T3: 10; N0: 43; N1-N3: 26	TCb + ddAC	24 (35.8), 20%, HE	pCR, ypT0/is, ypN0	36 (53.7)	14 (58.3) *vs* 22 (51.2)	NR
Abuhadra *et al* [15], America	NR	2015.10-2020.10	408	51 (23–77)	I: 41, II: 284, III: 83	AC→TCb	143 (35.0), 20%, HE	pCR, ypT0/is, N0	166 (40.7)	85 (59.4) *vs* 81 (30.6)	NR
Asano *et al*[31], Japan	Retrospective cohort	2007-2013	61	NR	T1: 24; T2-T4: 153; N0: 41; N1-N3: 136	FEC→T	48 (78.7), 10%, HE	pCR, ypT0	28 (45.9)	26 (54.2) *vs* 2 (15.4)	NR
Ono *et al*[54],	NR	1999-2007	92	52 (23-76)	II: 23, III: 36;	AC→T	67 (72.8)[1], high: (3-5),	pCR, ypT0	29 (31.5)	25 (37.3) *vs* 4	NR

Japan						CEF	HE			(16.0)	
Wang *et al*[35], America	NR	2007-2014	72	NR	T1: 5; T2: 48; T3: 15; T4: 5; N0: 38; N1-N3: 34	NR	53 (1/52) (73.6), (50%) 10%, HE	pCR, ypT0	38 (52.8)	35 (66.0) *vs* 3 (15.8)	NR
Dong *et al*[29], ChiNR	Retrospective cohort	2010.1-2014.12	170	NR	T1-2: 110; T3-4: 60	TAC	122 (74/48) (71.8), (20%) 10%, HE	pCR, ypT0 DFS OS	48 (28.2)	38 (31.1) *vs* 10 (24.8)	NR
Würfel *et al* [44], Germany	NR	2015.5-2017.4	146	NR	T1: 59; T2-T4: 90	NR	24 (16.4), 50%, HE	pCR ypT0 ypN0	56 (38.4)	16 (66.7) *vs* 40 (32.8)	NR
Hamy *et al*[42], France	NR	2015.1-2017.3	717	NR	T1-T2: 529; T3: 189; N0: 282; N1-N3: 435	NR	81 (11.3), 50%, HE	pCR, ypT0	202 (28.2)	48 (59.2) *vs* 154 (24.2)	OR: [U] 5.02 (4.27-5.77), 0.001
Cerbelli *et al*[41], Italy	Retrospective consecutive cohort	NR	59	49 (28-74)	II: 36, III: 24	NR	17 (28.8), 50%, HE	pCR, ypT0	22 (37.3)	13 (76.5) *vs* 9 (21.4)	NR

[1]High: Tumor-infiltrating lymphocyte proportion > 10% (2 points) combined with mild (1 point) or marked (2 points) intensity.

DFS: Disease-free survival; HE: Hematoxylin eosin staining; IPD: Individual patient data; M: Multivariate analysis; NR: Not reported; OR: Odds ratio; OS: Overall survival; pCR: Pathological complete response; RCT: Randomized controlled trial; RR: Risk ratio; TIL: Tumor-infiltrating lymphocyte; U: Univariate analysis.

International TILs Working Group in 2014[26], while five studies[27-30] did not report the specific method used for TIL assessment. The cutoff value for TIL level most commonly reported was 10% (n = 10)[18,29,31-38], followed by 50% (n = 8)[17,27,39-44], 20% (n = 4)[15,16,45,46], 30% (n = 3)[17,28,47], 40% (n = 3)[48-50], and 60% (n = 2)[51,52].

Association between preoperative TIL levels and therapeutic efficacy of NAT in TNBC patients

Overall meta-analysis: A meta-analysis of 32 studies revealed that the patients with high TIL levels had a high proportion of pCR events (46.7%, 1004/2092) than patients with low TIL levels (26.4%, 900/3254) with a significant difference (P < 0.001, REM, I^2 = 56%) (Figure 2). Sensitivity analysis using leave-one-out approach indicated that the meta-analytical statistics were not changed by any single study: Excluding the study with the largest effect size[32], the calculated RR was 1.99 (95%CI: 1.75-2.26, REM, I^2 = 55%).

Publication bias analysis: An asymmetric funnel plot and Egger's test P value (P = 0.001) less than 0.05 suggested potential publication bias in the included studies of overall meta-analysis. Additionally, the trim-and-fill method was further employed for assessing and adjusting for publication bias, the analytical result showed that nine missing studies were interpolated during the analysis to account for potential bias. It was observed that there was no significant asymmetry in the trimmed funnel plot and still significant overall meta-analytical effect size after adjusting for publication bias, suggesting that there was limited or insignificant publication bias (Figure 3).

Subgroup analysis: Due to significant heterogeneity among the included studies in the overall meta-analysis, subgroup analysis was conducted based on important variables, including study design, TIL cutoff value, sample size, and geographical region, to explore the sources of between-study heterogeneity. The analytical results indicated that the statistical effect sizes of all subgroup analyses were consistent with the overall meta-analysis results, and there were no

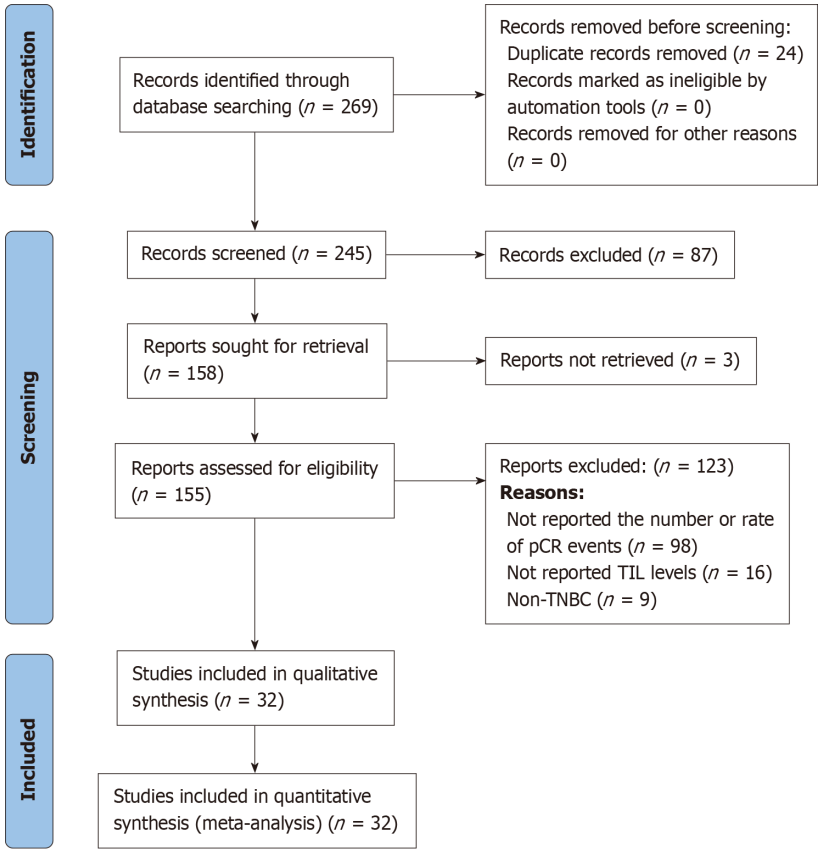

Figure 1 PRISMA flow diagram for study selection of systematic review and meta-analysis. pCR: Pathological complete response; TIL: Tumor-infiltrating lymphocyte; TNBC: Triple-negative breast cancer.

significant differences in the statistics among the subgroups. However, there were noticeable differences in the heterogeneity among the subgroups. Subgroup analysis revealed that the sources of between-study heterogeneity could stem from the subgroup of retrospective cohort studies (I^2 = 58%) (Figure 4), the subgroups with cutoff values of 40% (I^2 = 78%) and 20% (I^2 = 67%), the subgroup with sample sizes > 80 (I^2 = 69%), and the subgroup with European populations (I^2 = 77%) (Table 2).

Meta-analysis of different NAT regimens

Among the 32 studies, except for five studies[35,41-44] without a description of the NAT regimen, the reported NAT regimens in 27 included 14 studies with anthracycline combined with cyclophosphamide (AC) followed by sequential paclitaxel (T) (AC-T) [15,17,18,32,36,37,39,40,47-50,52,53], three studies with AC followed by sequential T in combination with anti-HER2 targeted therapy (AC-T + targeted therapy)[16,33,38], four studies with AC followed by sequential T in combination with platinum (Cb) agents (AC-TCb)[34,45,46,51], two studies with AC followed by sequential T in combination with fluorouracil (Fu) (AC-T + Fu)[31,54], and four studies with AC combined with T (TAC)[27-30].

The included studies were analyzed according to the NAT regimens, and the results revealed that patients with high TIL levels in different NAT regimens, such as AC-T, AC-TCb, AC-T + targeted therapy, AC-T + FU, and TAC, had 1.57 to 2.75 times greater rates of pCR events than those with low TIL levels. Moreover, there was no significant difference in the statistics among the various NAT regimens (P = 0.29). The detailed meta-analysis data of TILs associated with treatment response to different NAT regimens in TNBC patients are presented in Figure 5 and Table 2.

DISCUSSION

Tumor immunity plays a crucial role in the body's defense against tumors and in mediating the response to anti-cancer treatments. The presence of TILs in breast tumors has been associated with improved clinical outcomes[55]. The role of TILs in the NAT response in TNBC patients has been extensively studied. Based on the existing studies evaluating the correlation between TIL assessment and NAT treatment outcomes in TNBC patients, we conducted a systematic review and meta-analysis of the relationship between TIL status and the response to NAT in TNBC patients. The results showed that TNBC patients with high levels of TILs had greater NAT pCR rates than did those with low TIL levels. Furthermore, analysis based on different NAT regimens revealed that TIL levels were significantly associated with treatment response in all NAT regimens incorporating anthracycline combined with taxane drugs. This suggests that TILs have predictive

Table 2 Subgroup analysis examining heterogeneity among the included studies

Analysis	No. of studies	Risk ratio (95%CI)	I^2 statistic (%)	*P* value for heterogeneity	Analytical model	*P* value for subgroup differences
Study design						
RCT	5	1.42 (1.23-1.64)	41	0.15	FEM	
Prospective cohort	2	2.24 (1.77-2.83)	0	0.64	FEM	
Retrospective cohort	18	2.27 (1.84-2.80)	58	0.01	REM	
Not reported	7	2.05 (1.77-2.36)	45	0.09	FEM	0.02
Cut-off						
60%	2	2.01 (1.57-2.58)	0	0.90	FEM	
50%	8	2.31 (1.95-2.74)	0	0.71	FEM	
40%	3	3.06 (1.60-5.84)	78	0.01	REM	
30%	3	2.33 (1.61-3.37)	46	0.16	FEM	
20%	4	1.68 (1.29-2.20)	67	0.03	REM	
10%	10	1.63 (1.24-2.15)	49	0.04	REM	
Locations						
Asia	12	1.90 (1.62-2.24)	46	0.04	FEM	
Europe	11	2.07 (1.58-2.71)	77	0.01	REM	
Americas	9	2.01 (1.76-2.30)	34	0.14	FEM	0.35
Sample size						
$n \leq 80$	16	2.62 (2.14-3.20)	35	0.08	FEM	
$n > 80$	16	1.82 (1.56-2.12)	69	0.01	REM	0.04
NAT regimens						
AC-T	14	2.13 (1.72-2.63)	56	0.01	REM	
TAC	4	1.99 (1.43-2.75)	0	0.44	FEM	
AC-T + targeted therapy	3	1.73 (1.12-2.67)	82	0.01	REM	
AC-TCb	4	1.57 (1.31-1.90)	43	0.15	FEM	
AC-T + Fu	2	2.75 (1.28-5.92)	0	0.61	FEM	0.02

AC: Anthracycline combined with cyclophosphamide; AC-T: Anthracycline combined with cyclophosphamide followed by paclitaxel or docetaxel; AC-T + Fu: Anthracycline combined with cyclophosphamide followed by paclitaxel or docetaxel, and fluorouracil; AC-TCb: Anthracycline combined with cyclophosphamide followed by paclitaxel or docetaxel, and platinum; FEM: Fixed-effects model; NAT: Neoadjuvant therapy; TAC: Paclitaxel or docetaxel combined with anthracycline, and cyclophosphamide; REM: Random-effects model.

value for treatment response in these NAT regimens. To our knowledge, this is the first comprehensive and specific evaluation of the ability of TILs to predict the response of TNBC patients to NAT, which offers important insights into predicting treatment response based on pretreatment tumor immune status in TNBC patients.

TILs play a vital role in the surveillance and defense against tumors within the tumor immune microenvironment. The positioning, clustering, interaction, and costimulation of TIL subgroups are crucial for effective antitumor immune responses[13]. TILs can directly eliminate cancer cells through various mechanisms, including the specific recognition of endogenous antigen peptide-MHC class I molecule complexes by CD8+ T cells, the secretion of substances such as perforin and granzymes to induce tumor cell death through proteolytic activity, and the expression of FasL or the secretion of tumor necrosis factor (TNF)-alpha to induce apoptosis in cancer cells by binding to the death receptor Fas and TNF receptor on the surface of target cells[56]. Studies have shown that chemotherapy drugs can not only directly kill cancer cells through cytotoxic effects but also regulate TILs to eliminate cancer cells. For example, T cells pretreated with doxorubicin, cyclophosphamide, and paclitaxel in a coculture system with tumor organoids showed a greater proportion of cancer cell apoptosis than did T cells that were only pretreated with doxorubicin and cyclophosphamide and cocultured with tumor organoids. In another study, no significant difference was observed in T-cell pretreatment between doxorubicin, cyclophosphamide, and carboplatin combination therapy and doxorubicin and cyclophosphamide alone.

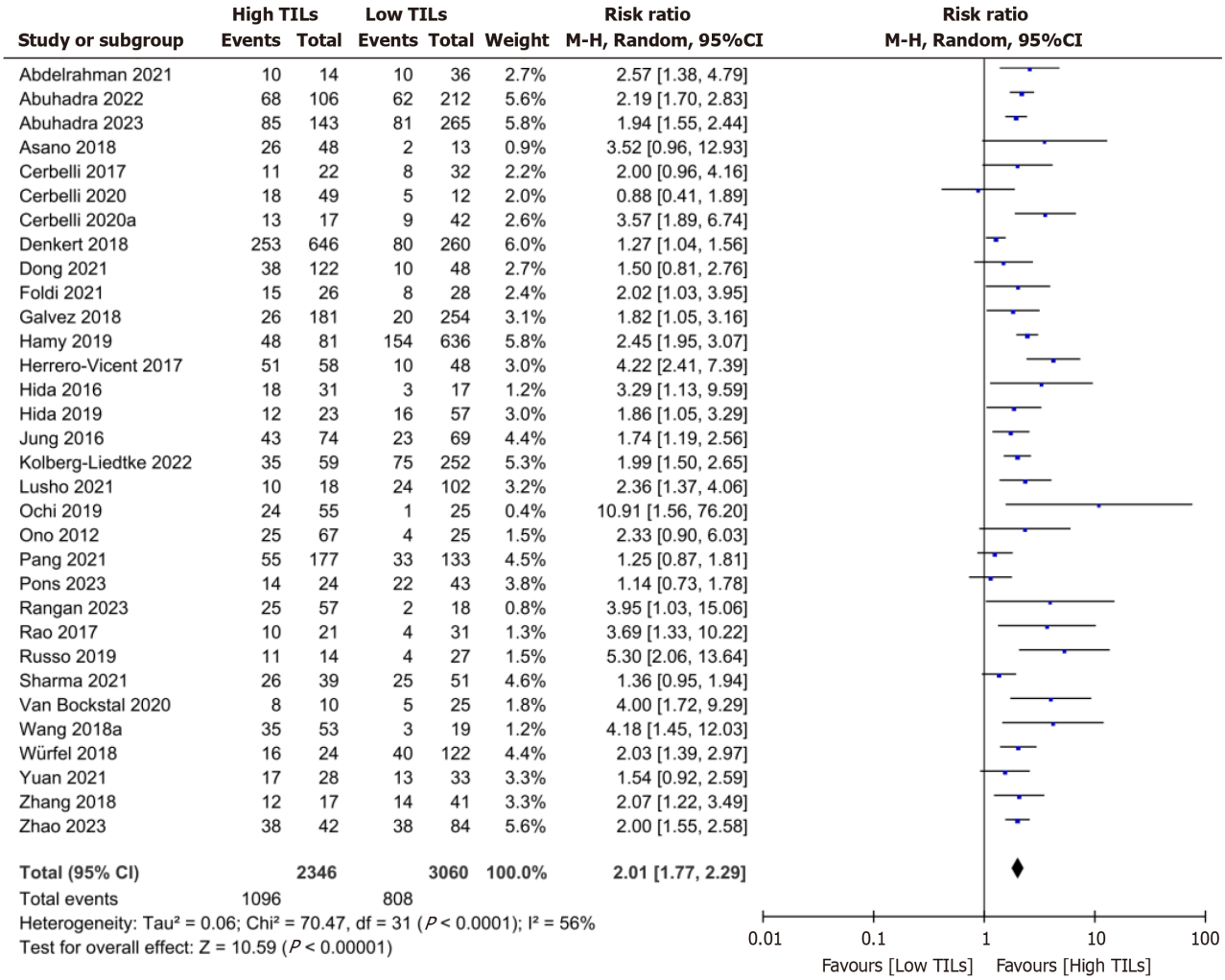

Figure 2 Forest plot demonstrating the correlation between tumor-infiltrating lymphocyte levels and the pathological complete response rate in triple-negative breast cancer patients receiving neoadjuvant therapy. TIL: Tumor-infiltrating lymphocyte.

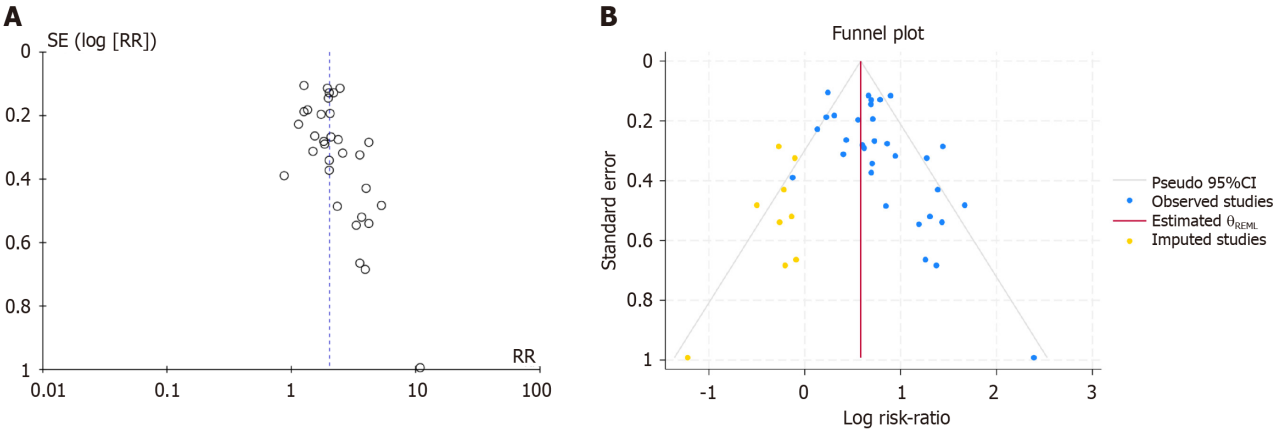

Figure 3 Funnel plot illustrating the correlation between tumor-infiltrating lymphocyte levels and the pathological complete response rate in studies investigating neoadjuvant therapy in triple-negative breast cancer patients. A: An asymmetric funnel plot and Egger's test *P* value (*P* = 0.001) less than 0.05 suggested potential publication bias in the included studies of overall meta-analysis; B: Trim-and-fill method showed that there was no significant asymmetry in the trimmed funnel plot and still significant overall meta-analytical effect size after adjusting for publication bias, suggesting that there was limited or insignificant publication bias.

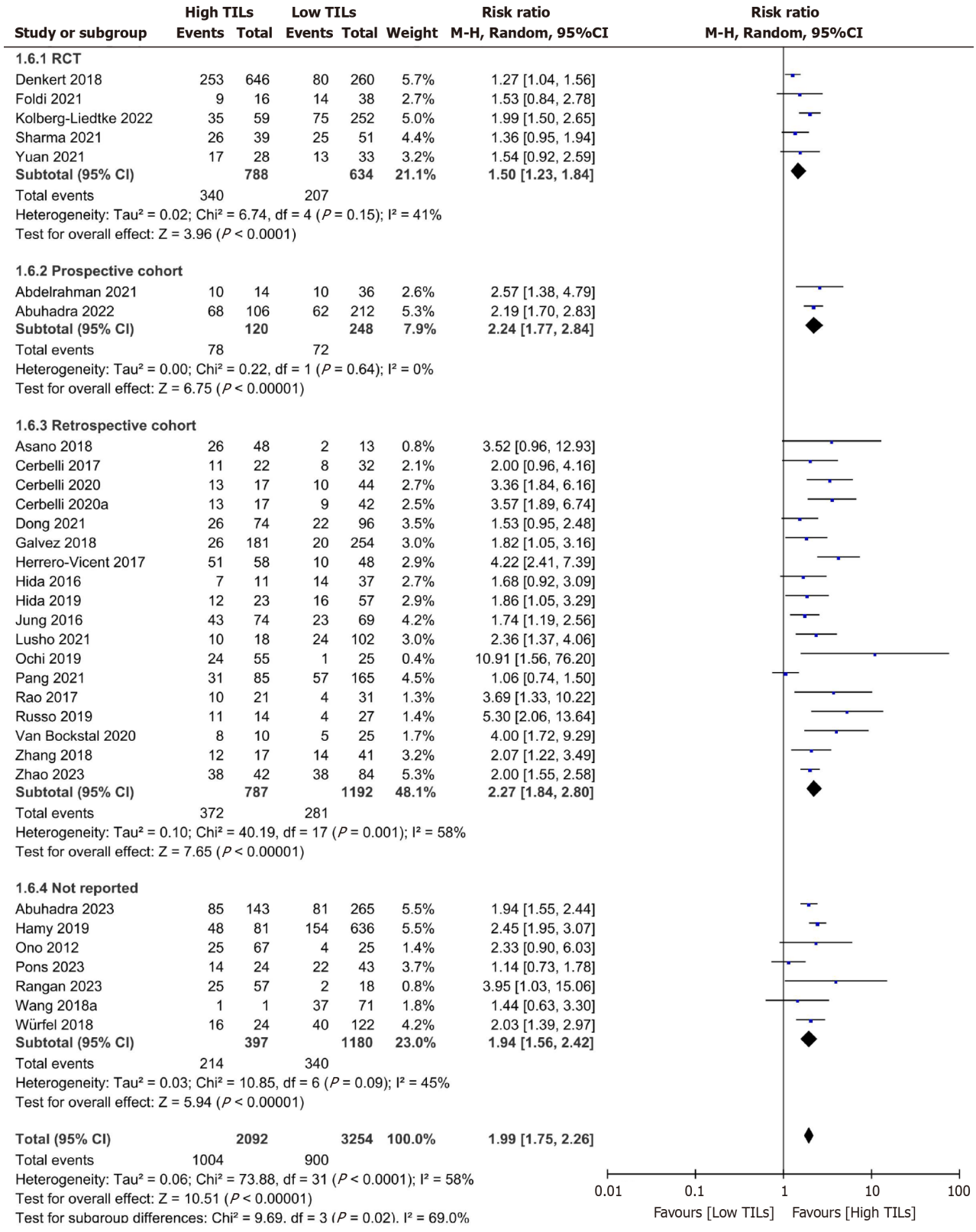

Figure 4 Forest plot illustrating subgroup analysis based on study design of included meta-analysis. TIL: Tumor-infiltrating lymphocyte; RCT: Randomized controlled trial.

This suggests that paclitaxel can modulate the cytotoxicity of T cells and exert an antitumor effect[57]. Furthermore, research has shown that BC patients with higher levels of TILs have better clinical responses to chemotherapy containing paclitaxel than to adjuvant chemotherapy regimens without taxanes, confirming this concept at the clinical level[58].

The systematic assessment and meta-analysis conducted herein provide substantial evidence that TNBC patients exhibiting high TIL levels exhibit superior treatment responses regardless of the specific NAT scheme employed, particularly in terms of higher pCR rates. Moreover, an increase in the TIL level following NAT treatment is associated with improved therapeutic outcomes in BC patients. The study findings indicate that the administration of anthracycline-

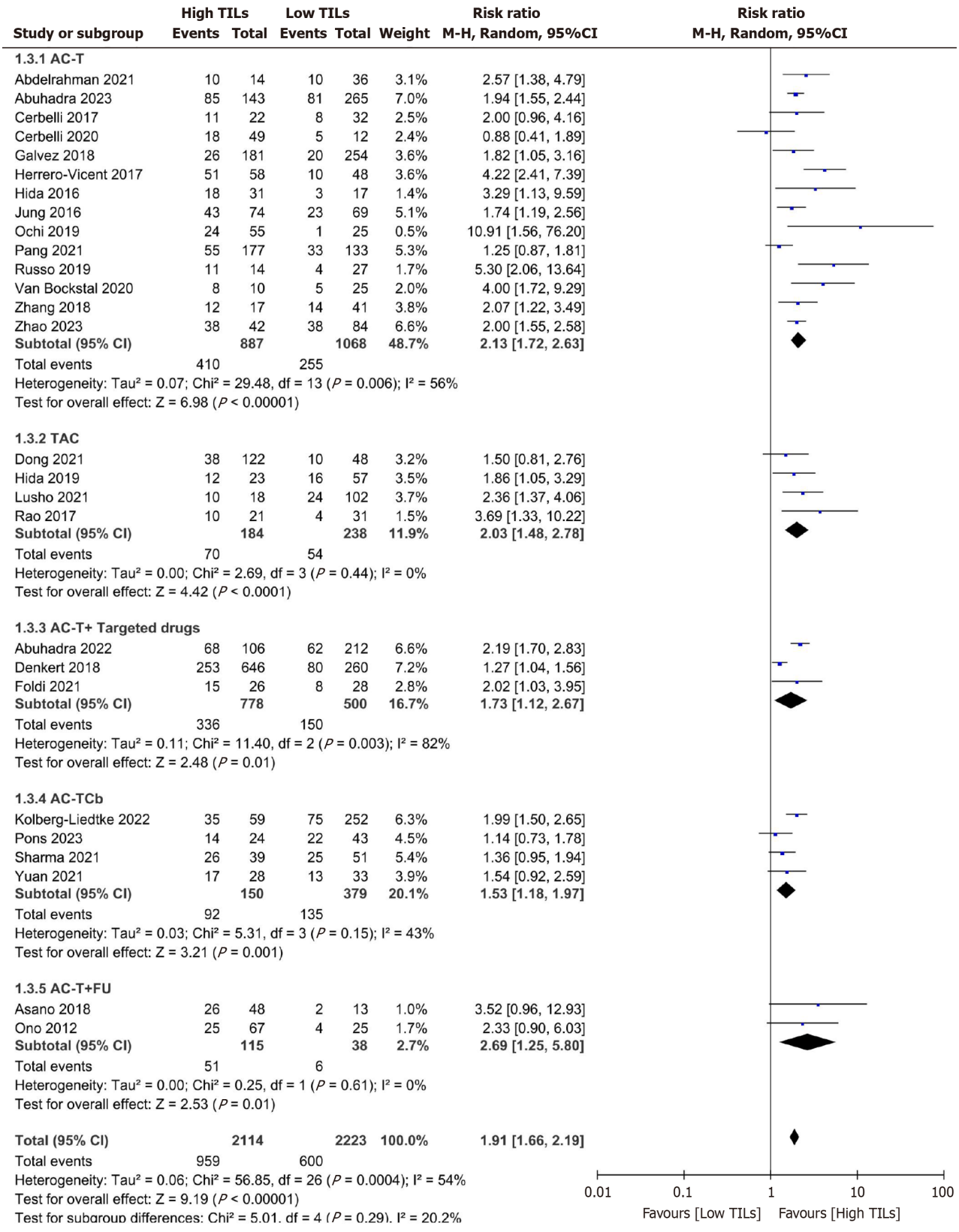

Figure 5 Forest plot illustrating the correlation between tumor-infiltrating lymphocyte levels and pathological complete response rates across various neoadjuvant therapy regimens. TIL: Tumor-infiltrating lymphocyte; AC: Anthracycline combined with cyclophosphamide; AC-T: Anthracycline combined with cyclophosphamide followed by paclitaxel or docetaxel; TAC: Paclitaxel or docetaxel combined with anthracycline, and cyclophosphamide; AC-TCb: Anthracycline combined with cyclophosphamide followed by paclitaxel or docetaxel, and platinum; AC-T + Fu: Anthracycline combined with cyclophosphamide followed by paclitaxel or docetaxel, and fluorouracil.

based chemotherapy drugs along with cyclophosphamide augments TIL levels in BC patients receiving NAT, and this increase in TIL levels is positively correlated with an improved pCR rate[33,59]. A study that stratified TNBC cohorts into lymphocyte-predominant BC (LPBC) and non-LPBC based on stromal TIL levels revealed that higher levels of stromal TILs in TNBC patients not only correlated with a greater pCR rate but also supported a greater pCR rate in LPBC patients than in non-LPBC patients. Additionally, even within the LPBC subgroup, the inclusion of platinum-based drugs in anthracycline-based chemotherapy followed by sequential paclitaxel yielded more significant benefits than in non-LPBC patients[60]. These clinical findings have been validated in various established experimental models of carcinogen-induced BC. In these animal models, the administration of doxorubicin amplifies the tumor antigen-specific proliferation of CD8+ T cells in tumor-draining lymph nodes in a homologous antigen-specific manner. Furthermore, it augments the ratio of CD8+ T cells infiltrating the tumor tissue and elicits tumor antigen-specific interferon-gamma production by these CD8+ TILs. Ultimately, the therapeutic effects of doxorubicin are mediated through these two mechanisms[61].

Due to the substantial heterogeneity observed in the meta-analysis of the 32 eligible studies, we performed subgroup analysis to investigate the sources of heterogeneity. The subgroup analysis showed that TNBC patients with high preoperative TIL counts exhibited increased pCR rates, irrespective of the study design. However, there were significant variations in heterogeneity among the different subgroups. In particular, the subgroup of randomized controlled trials and prospective cohort studies showed no interstudy heterogeneity, whereas the subgroup of retrospective cohort studies demonstrated considerable interstudy heterogeneity. Therefore, the primary contributor to the interstudy heterogeneity among the overall meta-analysis was attributed to the included retrospective cohort studies. These findings highlight the essential requirement for rigorous and well-designed research, including prospective designs and/or randomized controlled designs in future research protocols, to ensure the consistency and accuracy of clinical trial outcomes. Consequently, when assessing the predictive value of TILs for TNBC NAT treatment response, the meta-analysis results from the subgroup of randomized controlled trials and prospective cohort studies, which exhibit good consistency, can be considered robust evidence for clinical decision-making. Additionally, subgroup analysis was performed to explore the influence of high TIL cutoff values, the source of the study population, and the median sample size on the heterogeneity observed in the current meta-analysis. The analytical results presented that the differences in the cutoff values and the source of the study population were also potential sources of interstudy heterogeneity. Sensitivity analysis, carried out by sequentially excluding individual studies from the overall meta-analysis results, showed that the overall findings were not affected by any single study, but the heterogeneity varied. Notably, exclusion of the study conducted by Denkert *et al* [33] resulted in the lowest level of heterogeneity (I^2 = 45%).

Despite our comprehensive evaluation of the association between TIL levels in preoperative BC tissue treated with NATs and pCR in TNBC patients, our systematic review and meta-analysis has several limitations. First, the assessment of TILs is subjective, and there may be substantial variations in determining TIL levels among different studies due to the subjective judgments of various pathology experts. This subjectivity may impact the true relationship between TIL levels and treatment response and introduce heterogeneity across studies. Additionally, the analysis was limited by the paucity of studies that examined the correlation between TIL levels and NAT treatment response according to different molecular marker types of TILs. Consequently, it was not possible to more comprehensively conduct a subgroup analysis based on TIL molecular subtypes to explore the relationship between TIL levels and NAT treatment response. Finally, the restriction to studies published in English or Chinese may introduce language bias in this analysis. Therefore, given these considerations, it is advisable to interpret the results of this meta-analysis with caution.

CONCLUSION

In summary, this systematic review and meta-analysis indicated that TNBC patients with elevated TILs exhibited significantly greater pCR after NAT than those with low TILs, even among different NAT regimens and in TNBC patients from diverse populations. Therefore, it can be concluded that high TIL levels in preoperative TNBC tissue have the potential to predict treatment response to various NAT regimens in all TNBC patients. Additionally, the subgroup analysis results of homogeneous randomized controlled trials support the use of high TIL levels as Class Ia clinical evidence to predict NAT treatment response in TNBC patients, and the results of homogeneous prospective cohort studies are classified as class 2a evidence. Therefore, in clinical practice, adopting appropriate threshold to define high levels of TILs can effectively predict the response to NAT and aid in making NAT decisions for TNBC patients.

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FOOTNOTES

Author contributions: Sun HK and Jiang WL acquisition of data, analysis, and interpretation of data, drafting the article, final approval; Zhang SL, Xu PC, and Wei LM interpretation of data, revising the article, final approval; Liu JB conception and design of the study, critical revision, final approval. Sun HK and Jiang WL contributed equally to this work as co-first authors. The reasons for designating

Sun HK and Jiang WL as co-first authors are as follows: First, Sun HK and Jiang WL spent equal time and effort on acquisition of data, analysis, and interpretation of data during the literature eligibility and data analytical process. Second, during the preparation of our manuscript, Sun HK and Jiang WL achieve equal contribution in drafting and final approval of article. Finally, co-first authorship of Sun HK and Jiang WL indicate that the two co-first authors have equal responsibilities and burdens associated with the quality and reliability of the article. In summary, we believe that designating Sun HK and Jiang WL as co-first authors for our manuscript is appropriate as it accurately reflects our team's collaborative spirit and equal contributions.

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Country of origin: China

ORCID number: Shi-Lei Zhang 0000-0001-6800-9464; Jiang-Bo Liu 0000-0002-1384-7353.

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