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Dissection of 4L lymph node for left-sided non-small cell lung cancer: a meta-analysis

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Background: The therapeutic efficacy of left lower paratracheal (4L) lymph node dissection in the management of left-sided non-small cell lung cancer (NSCLC) remains an unresolved clinical question. Therefore, we conducted a metaanalysis to compare the survival of patients with left-sided NSCLC who underwent 4L lymph node dissection (LND+) and those who did not (LND–).

Methods: Seven databases were searched for relevant studies comparing patients with left-sided NSCLC who underwent 4L lymph node dissection and those who did not. The primary endpoints were survival indicators, including overall survival (OS) and disease-free survival (DFS). Secondary endpoints included hospitalization and follow-up outcomes.

Results: After thoroughly screening 431 studies, six studies encompassing 4,253 patients were included in the final analysis. The LND+ group showed better OS (hazard ratio [HR]: 0.65 [0.52, 0.81], p < 0.0001) and DFS (HR: 0.82 [0.71, 0.95], p = 0.008). The 4L LND+ group also demonstrated higher OS rates at 1–5 years and DFS at 1 year. Postoperative complications and recurrence rates were similar between the two groups.

Conclusions: Based on these results, 4L lymph node dissection should be performed for left-sided resectable NSCLC, due to its association with improved OS and DFS.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/view/CRD42024567681, identifier CRD42024567681.

KEYWORDS

dissection, left, 4L lymph node, non-small lung cancer, meta-analysis

Introduction

Lung cancer continues to be a predominant contributor to cancer-related mortality globally (1–4). Among the subtypes of lung cancer, non-small cell lung cancer (NSCLC) accounts for the vast majority (approximately 85%) of all cases (5), and the 5-year survival rate across all stages is about 20% (6). So far, the standard treatment for early-stage NSCLC

is tumor resection and lymph node dissection (7), including mediastinal lymph node dissection and systemic lymph node sampling (4, 8, 9). The National Comprehensive Cancer Network (NCCN) guidelines recommend that mediastinal lymph node dissection should include no fewer than three stations (10–12).

However, the clinical necessity of left lower paratracheal (4L) lymph node dissection (LND) for left-sided NSCLC remains unclear (10). A previous study by Wang et al. (7) showed that station 4L lymph node involvement is common in the left-sided NSCLC, and that 4L LND can improve the prognosis of patients compared to those who did not undergo this procedure (7). Another study conducted by Zhao et al. (13) demonstrated that performing 4L lymph node dissection provides greater benefits to disease-free survival (DFS) and overall survival (OS) in patients with left-sided NSCLC. Yang et al. (14) also confirmed that 4L LND improves survival in left-sided NSCLC. Similarly, Gryszko et al. (15) indicated that the benefits of lymphadenectomy are particularly evident at the 4L lymph node station. However, Wo et al. (16) presented a differing perspective, finding that 4L LND does not improve patient survival and may instead increase postoperative complications (16).

To further confirm whether performing 4L lymph node dissection improves survival in left-sided NSCLC, we conducted a meta-analysis comparing survival outcomes between patients who underwent 4L LND and those who did not.

Materials and methods

Adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, this study was meticulously conducted (Supplementary Table S1; PROSPERO ID: CRD42024567681).

Search strategy

We systematically searched the databases PubMed, Web of Science, EMBASE, Cochrane Library, ScienceDirect, and Scopus up to 15 April 2025, to analyze the survival of patients with leftsided NSCLC. The following MeSH terms were used: "left-sided", "4L lymph node," and "lung cancer". References from the retrieved articles (including meta-analyses and abstracts) were also screened for additional eligible articles. Detailed search strategies are provided in Supplementary Table S2.

Selection criteria

Inclusion criteria were as follows:

- 1. Population: patients with left-sided NSCLC who underwent tumor resection and LND.
- 2. Intervention and comparison: patients who underwent 4L LND compared with those who did not.
- 3. Outcomes: OS, DFS, 1–5-year overall survival rates (1–5year OSR), 1–5-year disease-free survival rates (1–5-year DFSR), and adverse events (AEs).
- 4. Study design: high-quality cohort and retrospective studies.

Conference abstracts, articles without original data, animal experiments, and abstracts only were excluded.

Data extraction

Two investigators independently extracted the following data: publication year, first author, country, number of participants, tumor characteristics (location, pathological stage), study design, participants characteristics (sex, age), lymph node metastasis, TNM stage, antitumor efficacy indices (OS, DFS, 1–5-year OSR, 1–5-year DFSR), and AEs. Any disagreements were resolved by a third investigator.

Outcome assessment

We analyzed survival data (OS and DFS), as well as survival rates at 1–5 years (OSR and DFSR). In addition, subgroup analyses of OS and DFS were performed based on age, sex, and pathological TNM stage.

Quality assessment

We used the Newcastle-Ottawa Scale (NOS) to assess the quality of cohort studies, a tool specifically designed for evaluating nonrandomized studies in meta-analyses. The scale includes three items: selection of groups, comparability of groups, and assessment of outcomes. Scores for the included studies were calculated (Supplementary Table S3) and categorized into three levels: low (0–3), moderate (4–6), and high (7–9) quality (17).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to assess the quality of evidence for the results. This system evaluates five domains: imprecision, risk of bias, indirectness, inconsistency, and publication bias. The quality of evidence was classified into four levels: very low, low, moderate, and high (18) (Supplementary Table S4).

Statistical analysis

Review Manager 5.3 and STATA 12.0 were used to analyze the pooled data in this meta-analysis. Hazard ratios were used to

Abbreviations: 4L, left lower paratracheal; NSCLC, non-small cell lung cancer; LND, lymph node dissection; LND+, patients treating with lymph node dissection; LND–, patients without lymph node dissection; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; NCCN, The National Comprehensive Cancer Network; PRISMA, The Preferred Reporting Items for Systematic Reviews and Meta-Analyses; OSR, overall survival rate; DFSR, diseasefree survival rate; AEs, adverse effects; NOS, the Newcastle-Ottawa Scale; GRADE, The Grading of Recommendations Assessment, Development, and Evaluation; PSM, propensity score matching; LUL, left upper lobe; LLL, left lower lobe; MD, mean difference; RCTs, randomized controlled trials.



evaluate survival outcomes (OS and DFS). An HR > 1 favored the 4L LND– group. while an HR < 1 favored the 4L LND+ group. Heterogeneity was assessed using the I^2 statistic and the χ^2 test. A random-effects model was applied when significant heterogeneity was present ($I^2 > 50\%$ or p < 0.1); otherwise, a fixed-effects model was used. Begg's rank correlation and Egger's linear regression test were used to assess publication bias. p < 0.05 was considered statistically significant.

Result

Search results and study quality assessment

Figure 1 illustrates the entire process of literature screening for the meta-analysis. A total of 431 eligible studies were initially identified. After a systematic search, six studies involving 4,253 patients were included in the final analysis (1,986 patients in the 4L LND+ group and 2,267 patients in the 4L LND– group). Among these, five studies (7, 13, 14, 16, 22) were conducted in China, and one study (15) was conducted in Poland. All patients in the included studies underwent surgical resection. All of the included studies were retrospective cohort studies, and propensity score matching (PSM) was applied in each to minimize potential bias (sex, age, TNM stage, surgical procedure, tumor location, tumor size, histological type, etc.).

As for the NOS, PSM was performed in all of the included studies; thus, the groups in these studies were well-balanced. Therefore, the scores of the five included studies were all > 7, indicating high quality. The baseline characteristics of the included studies are presented in Table 1. The GRADE system showed that most of the studies were of high quality (Supplementary Table S4).

Survival

Five studies compared OS, showing high heterogeneity (p = 0.0009, $I^2 = 79$). The results indicated that, compared with the 4L LND– group, patients who underwent 4L lymph node dissection had significantly better OS (HR: 0.65 [0.52, 0.81], p < 0.0001) (Figure 2A). Subgroup analysis demonstrated that the 4L LND+ group achieved better OSR-1y (RR: 0.97 [0.95, 0.99], p = 0.006), OSR-2y (RR: 0.94 [0.91, 0.97], p < 0.0001), OSR-3y (RR: 0.90 [0.85, 0.95], p = 0.0004), OSR-4y (RR: 0.88 [0.84, 0.92], p < 0.0001), and OSR-5y (RR: 0.90 [0.85, 0.95], p < 0.0001) (Figure 3A, 4). With the prolongation of survival time, the advantage of OSR in the 4L LND + group became more apparent (Figure 5A). Subgroup analysis based on tumor location showed that in both the left upper lobe (LUL) and left lower lobe (LLL), the 4L LND+ group tended to achieve better 1–5-year OSR (Supplementary Figures S1A, B).

Two studies compared DFS (heterogeneity: p = 0.20, $I^2 = 38$). The results showed that the 4L LND+ group had better DFS (HR: 0.82 [0.71, 0.95], p = 0.008) (Figure 2B). Subgroup analysis indicated that the 4L LND+ group achieved better DFSR-1y (RR: 0.92 [0.88, 0.97], p = 0.0005), DFSR-2y (RR: 0.92 [0.81, 1.03], p = 0.16), DFSR-3y (RR: 0.92 [0.81, 1.04], p = 0.18), DFSR-4y (RR: 0.90 [0.76, 1.08], p = 0.25), and DFSR-5y (RR: 0.89 [0.67, 1.18], p = 0.42) (Figures 3B, 6). As survival time increased, the advantage of DFSR in the 4L LND+ group became more apparent (Figure 5B).

Subgroup analysis

We evaluated the possible factors that may affect the survival of the 4L LND+ group compared to the 4L LND– group in early-stage left-sided NSCLC. The results suggested that the 4L LND+ group had a more favorable impact on survival (Table 2).

Hospitalization and follow-up indicators

Postoperative hospital stay (mean difference [MD]: 0.32 [0.14, 0.50] days, p = 0.0005, Supplementary Figure S2) was similar

between the two groups. Postoperative complications are shown in Table 3. The results indicated that the incidence of complications was also similar between the two groups (RR: 1.45 [1.01, 2.08], p =0.04) (Supplementary Figure S3). Similarly, overall recurrences (RR: 0.49 [0.11, 2.24], p = 0.36), local LN recurrences (RR: 0.73 [0.47, 1.15], p = 0.17), and supraclavicular or cervical LN recurrences (RR: 0.79 [0.36, 1.71], p = 0.54) were not significantly different between the two groups (Supplementary Figure S4). Subgroup analysis showed that patients in the 4L LND+ group were more likely to experience locoregional recurrence, whereas patients in the 4L LND – group were more likely to experience distant metastasis or locoregional recurrence and distant metastasis (Supplementary Figure S5).

Occurrence

We analyzed the incidence and distribution of mediastinal lymph node metastasis according to tumor location. The results showed that station L4 had a similar occurrence rate between the LUL and LLL. Metastasis in stations 5 and 6 was more common in LUL, whereas stations 7 and 8 were more frequently involved in LLL (Table 4).

Sensitivity analysis

We performed sensitivity analyses for OS and DFS (Supplementary Figure S6). To assess the sensitivity and reliability of the results, we evaluated the impact of each study on the overall outcomes, which indicated that the OS and DFS findings were reliable and stable.

Publication bias

No publication bias was detected in OS and DFS (Supplementary Figure S7).

Discussion

Lung cancer remains a leading cause of cancer-related death worldwide (19). Among the various types, NSCLC accounts for a large proportion, representing approximately 80%–85% of all lung cancer cases (20). Currently, the standard treatment for resectable NSCLC is surgical resection combined with lymph node dissection (8, 9). However, for left-sided NSCLC, the necessity of dissecting the 4L lymph nodes remains clinically uncertain (10, 21, 22), with the exception of the European Society of Thoracic Surgeons guidelines, which recommend 4L LND for left-sided NSCLC (11). Therefore, we conducted a systematic review and meta-analysis to evaluate whether performing 4L lymph node dissection improves survival time and prognosis in patients with resectable left-sided NSCLC based on previous related studies. The results demonstrated that, compared to TABLE 1 Summary of baseline characteristics of the included studies.

Year	Author	Country	Treatment arms	Patients (<i>n</i>)	Age (mean, years)	Patients (n) after PSM	Sex (M/F)	Adjustment for con- founding factors	4L LN metastasis rate	Tumor type	pTNM stage	Follow-up time (m)	Study design
2023	Wu (22)	China	4L LND+; 4L LND–	119; 193	NA	119; 193	70/49; 17/76	Age, sex, smoking history, clinical stage, adjuvant therapy, tumor differentiation, and tumor size were well balanced between the two groups	9.2	NSCLC	I–III	77	Cohort study
2022	Wo (16)	China	4L LND+; L LND–	586; 54	50.4; 0.3	416; 16	278/138; 269/147	Sex, histologic subtype, T stage, age, smoking history, LVI status, location, APLN status, IMLN status, N1 LN status, and surgical procedure	16.6	NSCLC	I–III	77	Cohort study
2021	Gryszko (15)	Poland	4L LND+; L LND–	659; 4,710	62.4; 62.9	659; 659	489/170; 475/184	Age, sex, smoking history, histopathological recognition, stage of lung cancer, and pathological T stage	10	NSCLC	0–IIIB	60.8	Cohort study
2020	Yang (14)	China	4L LND+; 4L LND–	391; 1,538	58.8 ± 9.9; 59.3 ± 10.2	317; 17	214/103; 33/84	Sex, age, tumor location, tumor size, anatomical type, smoking history, and surgical procedure, histology, cell differentiation, adjuvant therapy, pT category, pN category, and the number of resected lymph nodes	11.8	NSCLC	T1- 4N0-M0	60 (range: 1-208)	Cohort study
2019	Zhao (13)	China	4L LND+; L LND–	460; 604	58.4	460; 460	309/151; 305/155	Age, sex, smoking history, tumor location, tumor size, histologic type, pathologic N (pN) stage, and surgical approach	14.6	NSCLC	I–IIIA	40	Cohort study
2018	Wang (7)	China	4L LND+; L LND-	139; 518	NA	134; 415	94/40; 284/131	Age, sex, pathological T (pT) stage, smoking history, pathological N (pN) stage, histology, tumor location, tumor area, and pathological tumor-node-metastasis (pTNM) stage	20.9	NSCLC	I–IIIB	99 (range: 4–153)	Cohort study

4L, left lower paratracheal; LND, lymph node dissection; LND+, patients with lymph node dissection; LND–, patients without lymph node dissection; PSM, propensity score matching; LVI, lymphovascular invasion; APLN, aortopulmonary zone lymph nodes; IMLN, inferior mediastinal lymph nodes; pTNM, pathological tumor node metastasis; NSCLC, non-small cell lung cancer.

A				Hazard Ratio	Hazaro	d Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% C	I IV, Rando	m, 95% Cl	
Wang 2018	-0.6162	0.0496	26.1%	0.54 [0.49, 0.60]			
Wo 2022	-0.1625	0.1214	20.6%	0.85 [0.67, 1.08]	•	-	
Wu 2023	-0.755	0.2123	13.6%	0.47 [0.31, 0.71]			
Yang 2020	-0.3857	0.1468	18.5%	0.68 [0.51, 0.91]	-		
Zhao 2019	-0.2877	0.1139	21.3%	0.75 [0.60, 0.94]			
Total (95% CI)			100.0%	0.65 [0.52, 0.81]	•		
		- 4 (D -	0.0000	2 - 70%			
Heterogeneity: Tau ² =	0.04; Chi ² = 18.63, df	= 4 (P =	0.0009), 1	- 1970			100
Heterogeneity: Tau ² = Test for overall effect:	0.04; Chi² = 18.63, df Z = 3.90 (P < 0.0001)	= 4 (P =	0.0009), 1	- 79%	0.01 0.1 ⁴ Favours [4L LND+]	l 10 Favours [4L	100 [LND-]
Heterogeneity: Tau ² = Test for overall effect:	0.04; Chi² = 18.63, df Z = 3.90 (P < 0.0001)	= 4 (P =	0.0009), 1	Hazard Ratio	0.01 0.1 favours [4L LND+]	I 10 Favours [4L Ratio	100 LND-]
Heterogeneity: Tau ² = Test for overall effect: . B Study or Subgroup	0.04; Chi ² = 18.63, df Z = 3.90 (P < 0.0001) log[Hazard Ratio]	= 4 (P =] SE	: Weight	Hazard Ratio	0.01 0.1 Favours [4L LND+] Hazard IV, Fixed	I 10 Favours [4L Ratio	100 LND-]
Heterogeneity: Tau ² = Test for overall effect: . B <u>Study or Subgroup</u> Wang 2018	0.04; Chi ² = 18.63, df Z = 3.90 (P < 0.0001) log[Hazard Ratio] -0.4005	= 4 (P = <u> SE</u> 0.1392	Weight 28.6%	Hazard Ratio IV, Fixed, 95% CI 0.67 [0.51, 0.88]	0.01 0.1 Favours [4L LND+] Hazard IV, Fixed	l 10 Favours [4L Ratio <u>, 95% Cl</u>	100 LND-]
Heterogeneity: Tau ² = Test for overall effect: . B <u>Study or Subgroup</u> Wang 2018 Wo 2022	0.04; Chi ² = 18.63, df Z = 3.90 (P < 0.0001) <u>log[Hazard Ratio]</u> -0.4005 -0.0943	= 4 (P = 0.1392 0.0987	Weight 28.6% 56.8%	Hazard Ratio IV. Fixed, 95% CI 0.67 [0.51, 0.88] 0.91 [0.75, 1.10]	0.01 0.1 Favours [4L LND+] Hazard IV, Fixed	l 10 Favours [4L Ratio <u>, 95% Cl</u>	100 LND-]
Heterogeneity: Tau ² = Test for overall effect: . B Study or Subgroup Wang 2018 Wo 2022 Zhao 2019	0.04; Chi ² = 18.63, df Z = 3.90 (P < 0.0001) <u>log[Hazard Ratio]</u> -0.4005 -0.0943 -0.1985	= 4 (P = 0.1392 0.0987 0.1946	Weight 28.6% 56.8% 14.6%	Hazard Ratio IV, Fixed, 95% CI 0.67 [0.51, 0.88] 0.91 [0.75, 1.10] 0.82 [0.56, 1.20]	0.01 0.1 Favours [4L LND+] Hazard IV, Fixed	I 10 Favours [4L Ratio I <mark>, 95% CI</mark>	100 LND-]
Heterogeneity: Tau ² = Test for overall effect: . B Study or Subgroup Wang 2018 Wo 2022 Zhao 2019 Total (95% CI)	0.04; Chi ² = 18.63, df Z = 3.90 (P < 0.0001) <u>log[Hazard Ratio]</u> -0.4005 -0.0943 -0.1985	= 4 (P = 0.1392 0.0987 0.1946	Weight 28.6% 56.8% 14.6% 100.0%	Hazard Ratio IV, Fixed, 95% Cl 0.67 [0.51, 0.88] 0.91 [0.75, 1.10] 0.82 [0.56, 1.20] 0.82 [0.71, 0.95]	0.01 0.1 Favours [4L LND+] Hazard IV, Fixed	I 10 Favours [4L Ratio I, 95% CI	100 LND-]
Heterogeneity: Tau ² = Test for overall effect: . B <u>Study or Subgroup</u> Wang 2018 Wo 2022 Zhao 2019 Total (95% CI) Heterogeneity: Chi ² =	0.04; Chi ² = 18.63, df Z = 3.90 (P < 0.0001) <u>log[Hazard Ratio]</u> -0.4005 -0.0943 -0.1985 3.22, df = 2 (P = 0.20	= 4 (P = 0.1392 0.0987 0.1946 0): ² = 38	Weight 28.6% 56.8% 14.6% 100.0%	Hazard Ratio IV, Fixed, 95% Cl 0.67 [0.51, 0.88] 0.91 [0.75, 1.10] 0.82 [0.56, 1.20] 0.82 [0.71, 0.95]	0.01 0.1 Favours [4L LND+] Hazard IV, Fixed	I 10 Favours [4L Ratio I, 95% CI	100 LND-]
Heterogeneity: Tau ² = Test for overall effect: . B <u>Study or Subgroup</u> Wang 2018 Wo 2022 Zhao 2019 Total (95% CI) Heterogeneity: Chi ² = Test for overall effect:	0.04; Chi ² = 18.63, df Z = 3.90 (P < 0.0001) <u>log[Hazard Ratio]</u> -0.4005 -0.0943 -0.1985 3.22, df = 2 (P = 0.20 Z = 2.65 (P = 0.008)	= 4 (P = 0.1392 0.0987 0.1946 0); I ² = 38	Weight 28.6% 56.8% 14.6% 100.0%	Hazard Ratio IV, Fixed, 95% Cl 0.67 [0.51, 0.88] 0.91 [0.75, 1.10] 0.82 [0.56, 1.20] 0.82 [0.71, 0.95]	0.01 0.1 Favours [4L LND+] Hazard IV, Fixed 0.01 0.1 1	I 10 Favours [4L Ratio , 95% Cl	100 LND-]

Forest plots of OS (A) and DFS (B) comparing 4L LND+ and 4L LND-.



patients who did not undergo 4L lymph node dissection, those in the 4L LND+ group had significantly better OS and DFS. Additionally, the 1–5-year survival rates for both OS and DFS were higher in the 4L LND+ group. Postoperative hospital stay, complications, and overall recurrence rates were similar between the two groups.

Better survival was the most significant advantage observed in the 4L LND+ group compared to the 4L LND– group. The primary endpoints of this meta-analysis were OS and DFS. Patients who underwent 4L LND+ dissection demonstrated superior outcomes compared to those who did not. Five studies assessed OS, showing a

Study or Subgroup			4L LN			RISK RATIO	
3 1 1 OSP.1v	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
5.1.1 OSK-19							
Wang 2018	373	415	123	134	3.0%	0.98 [0.92, 1.04]	-
Wo 2022	383	416	395	416	6.4%	0.97 [0.94, 1.01]	-1
Wu 2023	182	193	112	119	2.2%	1.00 [0.95, 1.06]	+
Yang 2020	285	317	301	317	4.9%	0.95 [0.91, 0.99]	
Zhao 2019	414	460	423	460	6.8%	0.98 [0.94, 1.02]	.
Subtotal (95% CI)		1801		1446	23.3%	0.97 [0.95, 0.99]	♦
Total events	1637		1354				
Heterogeneity: Chi ² = 2	2.60. df = 4	4 (P = 0	.63): I ² =	0%			
Test for overall effect:	Z = 2.74 (I	P = 0.00)6)	070			
3.1.2 OSR-2v							
Wang 2018	307	415	109	134	2 7%	0 91 [0 82 1 00]	
Wo 2022	3/1	416	354	416	5 7%	0.06 [0.02, 1.00]	
Wu 2022	171	410	110	410	0.7 /0		
Wu 2023	1/1	193	005	119	2.2%	0.90 [0.69, 1.03]	
Tang 2020	250	317	285	317	4.0%	0.06 [0.82, 0.94]	_ +
Znao 2019	363	460	377	460	6.1%	0.96 [0.90, 1.03]	
Subtotal (95% CI)		1801		1446	21.3%	0.94 [0.91, 0.97]	▼
Total events Heterogeneity: Chi ² = 5	1432 5.86, df = 4	4 (P = 0	1235 .21); I² =	32%			
Test for overall effect:	Z = 3.97 (I	□ < 0.00	001)				
3.1.3 OSR-3y						Modified by Ran	dom-effects models
Wang 2018	266	415	105	134	2.8%	0.82 [0.73, 0.9	2]
Wo 2022	324	416	333	416	4.6%	0.97 [0.91, 1.0	14] -+
Wu 2023	155	193	102	119	3.3%	0.94 [0.85, 1.0	µ4] ─-+
Yang 2020	228	317	260	317	3.9%	0.88 10.80.09	ai ———
Zhao 2019	313	460	359	460	4.2%	0.87 10 81 0 9	41
2	010		555	4440	19.0%		51 🔶
Subtotal (95% CI)		1801		144n	10,2176	0.90 10 65.0 9	
Subtotal (95% CI) Total events	1286	1801	1159	1440	10.376	0.90 [0.65, 0.9	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2	1286 0.00; Chi² Z = 3.53 (I	1801 = 9.00, P = 0.00	1159 df = 4 (F 004)	1446 9 = 0.06	5); I ² = 56%	0.90 [0.65, 0.9	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2 3.1.4 OSR-4y	1286 0.00; Chi² Z = 3.53 (I	1801 = 9.00, P = 0.00	1159 df = 4 (F 004)	1446 9 = 0.06	3); I² = 56%	0.au [0.63, 0.a	
Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: 2 3.1.4 OSR-4y Wang 2018	1286 0.00; Chi² Z = 3.53 (I 224	1801 = 9.00, P = 0.00 415	1159 df = 4 (F 004) 91	1446 9 = 0.06 134	10.3 % 5); I² = 56% 2.2%	0.30 [0.83, 0.9	
Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022	1286 0.00; Chi² Z = 3.53 (I 224 295	1801 = 9.00, P = 0.00 415 416	1159 df = 4 (F 004) 91 320	1446 9 = 0.06 134 416	10.3 % 5); I² = 56% 2.2% 5.2%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00]	
Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023	1286 0.00; Chi² Z = 3.53 (I 224 295 141	1801 = 9.00, P = 0.00 415 416 193	1159 df = 4 (F 004) 91 320 93	1446 9 = 0.06 134 416 119	10.9 % 6); I ² = 56% 2.2% 5.2% 1.9%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82 1.06]	
Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yaan 2020	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216	1801 = 9.00, P = 0.00 415 416 193 317	1159 df = 4 (F 004) 91 320 93 247	1446 9 = 0.06 134 416 119 317	10.9 % 2.2% 5.2% 1.9% 4.0%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.22, 0.96]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Theo 2010	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285	1801 = 9.00, P = 0.00 415 416 193 317 460	1159 df = 4 (F 004) 91 320 93 247 231	1446 9 = 0.06 134 416 119 317	10.9 % 2.2% 5.2% 1.9% 4.0%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI)	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285	1801 = 9.00, P = 0.00 415 416 193 317 460	1159 df = 4 (F 004) 91 320 93 247 331	1446 9 = 0.06 134 416 119 317 460	10.3% 2.2% 5.2% 1.9% 4.0% 5.3%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.86 [0.79, 0.94]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI)	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285	1801 = 9.00, P = 0.00 415 416 193 317 460 1801	1159 df = 4 (F)04) 91 320 93 247 331	134 134 416 119 317 460 1446	10.3 % 2.2% 5.2% 1.9% 4.0% 5.3% 18.6%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.86 [0.79, 0.94] 0.88 [0.84, 0.92]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: <i>i</i> 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161	1801 = 9.00, P = 0.00 415 416 193 317 460 1801	1159 df = 4 (F)04) 91 320 93 247 331 1082	134 134 416 119 317 460 1446	10.3 % 2.2% 5.2% 1.9% 4.0% 5.3% 18.6%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.94] 0.88 [0.84, 0.92]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 2	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = 4 Z = 5.48 (I	1801 = 9.00, P = 0.00 415 416 193 317 460 1801 4 (P = 0 P < 0.00	1159 df = 4 (F)04) 91 320 93 247 331 1082 .38); I ² =)001)	134 134 416 119 317 460 1446 5%	2.2% 5.2% 1.9% 4.0% 5.3% 18.6%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.86 [0.79, 0.92]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = / Test for overall effect: <i>J</i> 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: <i>J</i> 3.1.5 OSR-5y	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = 4 Z = 5.48 (I	1801 = 9.00, P = 0.00 415 416 193 317 460 1801 4 (P = 0 P < 0.00	1159 df = 4 (F)04) 91 320 93 247 331 1082 .38); I ² =)001)	1446 P = 0.06 134 416 119 317 460 1446 5%	2.2% 5.2% 1.9% 4.0% 5.3% 18.6%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.86 [0.79, 0.92]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = / Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 2 3.1.5 OSR-5y Wang 2012	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = 4 Z = 5.48 (I	1801 = 9.00, P = 0.00 415 416 193 317 460 1801 4 (P = 0 P < 0.00	1159 df = 4 (F 004) 91 320 93 247 331 1082 .38); I ² = 0001)	1446 P = 0.06 134 416 119 317 460 1446 5%	2.2% 5.2% 1.9% 4.0% 18.6%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.86 [0.79, 0.94] 0.88 [0.84, 0.92]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = / Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 2 3.1.5 OSR-5y Wang 2018 Wa 2022	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = <i>i</i> Z = 5.48 (I 199	1801 = 9.00, = 0.00 415 416 193 317 460 1801 4 (P = 0 = < 0.00 415	1159 df = 4 (F 004) 91 320 93 247 331 1082 38); I ² = 0001) 83	1446 2 = 0.06 134 416 119 317 460 1446 5% 134	2.2% 5.2% 1.9% 4.0% 5.3% 18.6%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.86 [0.79, 0.94] 0.88 [0.84, 0.92]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 3.1.5 OSR-5y Wang 2018 Wo 2022 Wu 2022	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = Z = 5.48 (I 199 283 283	1801 = 9.00, P = 0.00 415 416 193 317 460 1801 4 (P = 0 P < 0.00 415 415	1159 df = 4 (F)004) 91 320 93 247 331 1082 0.38); I ² = 0001) 83 291	1446 134 416 119 317 460 1446 5% 134 416	2.2% 5.2% 1.9% 4.0% 5.3% 18.6% 2.0% 4.7%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.94] 0.88 [0.84, 0.92] 0.77 [0.66, 0.91] 0.97 [0.89, 1.07]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 2 3.1.5 OSR-5y Wang 2018 Wo 2022 Wu 2023	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = Z = 5.48 (I 199 283 126	1801 = 9.00, P = 0.00	1159 df = 4 (F)004) 91 320 93 247 331 1082 .38); I ² =)001) 83 291 83	134 416 119 317 460 1446 5% 134 416 119	2.2% 5.2% 1.9% 4.0% 5.3% 18.6% 2.0% 4.7% 1.7%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.94] 0.88 [0.84, 0.92] 0.77 [0.66, 0.91] 0.97 [0.89, 1.07] 0.90 [0.78, 1.05]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = / Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 2 3.1.5 OSR-5y Wang 2018 Wo 2022 Wu 2023 Yang 2020	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = 4 Z = 5.48 (I 199 283 126 197	1801 = 9.00, P = 0.00	1159 df = 4 (F)004) 91 320 93 247 331 1082 .38); I ² =)001) 83 291 86 228	1344 134 134 134 416 119 317 460 1446 5% 134 416 119 317 134 317 317 134 317 134 137 137 137 146 119 317 146 119 317 146 119 317 146 119 317 146 119 317 146 119 317 146 119 317 146 119 317 146 146 119 317 146 146 146 146 146 146 146 146	2.2% 5.2% 1.9% 4.0% 5.3% 18.6% 2.0% 4.7% 1.7% 3.7%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.88 [0.84, 0.92] 0.88 [0.84, 0.92] 0.77 [0.66, 0.91] 0.97 [0.89, 1.07] 0.90 [0.78, 1.05] 0.86 [0.77, 0.96]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = / Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 2 3.1.5 OSR-5y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = 4 Z = 5.48 (I 199 283 126 197 262	1801 $= 9.00,$ 415 416 193 317 460 415 415 416 193 317 460	1159 df = 4 (F 004) 91 320 93 247 331 1082 .38); I ² = 0001) 83 291 86 228 290	1344 1344 134 134 416 119 317 460 1446 134 416 119 317 460	2.2% 5.2% 1.9% 4.0% 5.3% 18.6% 2.0% 4.7% 1.7% 3.7% 4.7%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.86 [0.79, 0.94] 0.88 [0.84, 0.92] 0.77 [0.66, 0.91] 0.97 [0.89, 1.07] 0.90 [0.78, 1.05] 0.86 [0.77, 0.86] 0.90 [0.81, 1.00]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = / Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 2 3.1.5 OSR-5y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI)	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = 4 Z = 5.48 (I 199 283 126 197 262	1801 = 9.00, > = 0.00 415 416 193 317 460 1801 4 (P = 0.00 415 416 193 317 460 183 415 416 193 317 460 1801	1159 df = 4 (F)04) 91 320 93 247 331 1082 .38); I ² = 0001) 83 291 86 228 290	1344 1344 134 139 1317 1460 1446 5% 134 416 119 317 460 1446 199 317 460 1446 199 1446 199 1467 199 197 197 197 197 197 197 19	2.2% 5.2% 1.9% 4.0% 5.3% 18.6% 2.0% 4.7% 1.7% 3.7% 4.7% 1.7%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.86 [0.79, 0.94] 0.88 [0.84, 0.92] 0.88 [0.84, 0.92] 0.97 [0.89, 1.07] 0.90 [0.78, 1.05] 0.86 [0.77, 0.96] 0.90 [0.81, 1.00] 0.90 [0.85, 0.95]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 2 3.1.5 OSR-5y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = Z = 5.48 (I 199 283 126 197 262 1067	1801 = 9.00, 415 416 193 317 460 1801 4 (P = 0 - < 0.0(415 416 193 317 460 1801	1159 df = 4 (F)004) 91 320 93 247 331 1082 .38); I ² =)001) 83 291 86 228 290 978	1344 1346 139 1317 460 1346 134 416 119 317 460 1446	2.2% 5.2% 1.9% 4.0% 5.3% 18.6% 2.0% 4.7% 1.7% 3.7% 4.7% 16.8%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.94] 0.88 [0.84, 0.92] 0.88 [0.84, 0.92] 0.97 [0.89, 1.07] 0.90 [0.78, 1.05] 0.90 [0.81, 1.00] 0.90 [0.85, 0.95]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 2 3.1.5 OSR-5y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6 Total events Heterogeneity: Chi ² = 6 Total events Heterogeneity: Chi ² = 6 Test for overall effect: 2	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = Z = 5.48 (I 199 283 126 197 262 1067 5.48, df = 4 Z = 4.02 (I	1801 $= 9.00, 0, 0 = 0.00$ 415 416 193 317 460 1801 $4 (P = 0)$ 415 416 193 317 460 1801 1801 $4 (P = 0)$ 400 1801	1159 df = 4 (F)04) 91 320 93 247 331 1082 .38); I ² = 0001) 83 291 86 228 290 978 .17); I ² = 001)	1344 134 416 19 317 460 1446 5% 134 416 119 317 460 1446 38%	2.2% 5.2% 1.9% 4.0% 5.3% 18.6% 2.0% 4.7% 1.7% 3.7% 4.7% 16.8%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.94] 0.88 [0.84, 0.92] 0.88 [0.84, 0.92] 0.97 [0.89, 1.07] 0.90 [0.78, 1.05] 0.90 [0.81, 1.00] 0.90 [0.85, 0.95]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = / Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 2 3.1.5 OSR-5y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6 Test for overall effect: 2 Total (95% CI)	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = 4 Z = 5.48 (I 199 283 126 197 262 1067 3.48, df = 4 Z = 4.02 (I	1801 $= 9.00,$ 415 416 193 317 460 1801 $4 (P = 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0$	1159 df = 4 (F)004) 91 320 93 247 331 1082 .38); I ² =)001) 83 291 86 228 290 978 .17); I ² =)01)	1344 134 416 119 317 460 1446 5% 134 416 119 317 460 1446 38% 7230	2.2% 5.2% 1.9% 4.0% 5.3% 18.6% 2.0% 4.7% 1.7% 3.7% 4.7% 16.8%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.86 [0.79, 0.94] 0.88 [0.84, 0.92] 0.88 [0.84, 0.92] 0.97 [0.89, 1.07] 0.90 [0.78, 1.05] 0.90 [0.78, 1.05] 0.90 [0.81, 1.00] 0.90 [0.85, 0.95]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 3.1.5 OSR-5y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6 Test for overall effect: Total (95% CI) Total events	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = 4 Z = 5.48 (I 199 283 126 197 262 1067 5.48, df = 4 Z = 4.02 (I 6583	1801 = 9.00, - = 0.00 415 416 193 317 460 1801 4 (P = 0 - < 0.00 415 416 193 317 460 1801 4 (P = 0 - < 0.00 415 416 193 317 460 1801 4 (P = 0 - < 0.00 4 (P = 0 - < 0.00 - < 0.00 4 (P = 0 - < 0.00 - < 0.00	1159 df = 4 (F)04) 91 320 93 247 331 1082 .38); I ² = 0001) 83 291 86 228 290 978 .17); I ² = 001) 5808	1344 134 416 119 317 460 1446 5% 134 416 119 317 460 1446 38% 7230	2.2% 5.2% 1.9% 4.0% 5.3% 18.6% 2.0% 4.7% 1.7% 3.7% 4.7% 16.8%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.86 [0.79, 0.94] 0.88 [0.84, 0.92] 0.77 [0.66, 0.91] 0.97 [0.89, 1.07] 0.90 [0.78, 1.05] 0.86 [0.77, 0.96] 0.90 [0.81, 1.00] 0.90 [0.85, 0.95]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: i^{2} 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: i^{2} 3.1.5 OSR-5y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6 Test for overall effect: i^{2} Total (95% CI) Total events Heterogeneity: Chi ² = 6 Total (95% CI) Total events Heterogeneity: Chi ² = 6	1286 $0.00; Chi^2$ Z = 3.53 (l) 224 295 141 216 285 1161 4.21, df = - Z = 5.48 (l) 199 283 126 197 262 1067 5.48, df = - Z = 4.02 (l) 6583 31.69, df = -	1801 $= 9.00, 0$ 415 416 193 317 460 1801 $4 (P = 0$ 415 416 193 317 460 1801 1801 $4 (P = 0$ 9005 $24 (P - 1)$	1159 df = 4 (F)04) 91 320 93 247 331 1082 (.38); I ² =)001) 83 291 86 228 290 978 .17); I ² =)01) 5808 < 0.0001	134 416 119 317 460 1446 5% 134 416 119 317 460 1446 38% 7230 ;; ² = 6	2.2% 5.2% 1.9% 4.0% 5.3% 18.6% 2.0% 4.7% 1.7% 3.7% 4.7% 16.8% 100.0%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.86 [0.79, 0.94] 0.88 [0.84, 0.92] 0.77 [0.66, 0.91] 0.97 [0.89, 1.07] 0.90 [0.78, 1.05] 0.86 [0.77, 0.96] 0.90 [0.81, 1.00] 0.90 [0.85, 0.95]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = : Test for overall effect: : 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: : 3.1.5 OSR-5y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6 Test for overall effect: : Total (95% CI) Total events Heterogeneity: Chi ² = 6 Test for overall effect: :	1286 0.00; Chi ² Z = 3.53 (I 224 295 141 216 285 1161 4.21, df = Z Z = 5.48 (I 199 283 126 197 262 1067 5.48, df = Z Z = 4.02 (I 6583 31.69, df = Z Z = 9.77 (I	1801 $= 9.00, 0$ 415 416 193 317 460 1801 $4 (P = 0$ 415 416 193 317 460 1801 $4 (P = 0$ $- 0.00$ 9005 $24 (P - 0.00$	1159 df = 4 (F)004) 91 320 93 247 331 1082 .38); I² =)001) 83 291 86 228 290 978 .17); I² =)01) 5808 < 0.0001)	134 416 119 137 460 1446 5% 134 416 119 317 460 1446 38% 7230 ; l ² = 6	2.2% 5.2% 1.9% 4.0% 5.3% 18.6% 2.0% 4.7% 1.7% 3.7% 4.7% 16.8%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.86 [0.79, 0.94] 0.88 [0.84, 0.92] 0.77 [0.66, 0.91] 0.97 [0.89, 1.07] 0.90 [0.78, 1.05] 0.90 [0.78, 1.05] 0.90 [0.85, 0.95] 0.92 [0.91, 0.94]	• • • • • •
Subtotal (95% CI) Total events Heterogeneity: Tau ² = / Test for overall effect: 2 3.1.4 OSR-4y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 2 3.1.5 OSR-5y Wang 2018 Wo 2022 Wu 2023 Yang 2020 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6 Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Chi ² = 6 Test for overall effect: 2 Test for suboroun diffe	1286 $0.00; Chi^2$ Z = 3.53 (l) 224 295 141 216 285 1161 4.21, df = - Z = 5.48 (l) 199 283 126 197 262 1067 5.48, df = - Z = 4.02 (l) 6583 61.69, df = Z = 9.77 (l)	1801 = 9.00, 2 = 0.00 415 416 193 317 460 1801 4 (P = 0 - < 0.00 415 416 193 317 460 1801 4 (P = 0 - < 0.00 9005 24 (P - 0 - < 0.00 9005	1159 df = 4 (F)004) 91 320 93 247 331 1082 .38); I² =)001) 83 291 86 228 290 978 .17); I² =)01) 5808 < 0.0001) .95, df =	134 416 119 316 1446 5% 134 416 119 317 460 1446 38% 7230 7230 ; ² = 6 4 (P <)	2.2% 5.2% 1.9% 4.0% 5.3% 18.6% 2.0% 4.7% 18.6% 1.7% 3.7% 4.7% 16.8% 100.0% 1%	0.79 [0.69, 0.92] 0.92 [0.85, 1.00] 0.93 [0.82, 1.06] 0.87 [0.79, 0.96] 0.86 [0.79, 0.94] 0.88 [0.84, 0.92] 0.77 [0.66, 0.91] 0.97 [0.89, 1.07] 0.90 [0.78, 1.05] 0.86 [0.77, 0.96] 0.90 [0.81, 1.00] 0.90 [0.85, 0.95] 0.92 [0.91, 0.94] = 84.6%	• • • • • • • • • • • • • • • • • • •

clear increase in survival for the 4L lymph node dissection group. Additionally, two studies compared DFS between the groups, with results indicating a tendency toward improved DFS in the 4L LND+ group. We also assessed the 1–5-year OS rate and DFS rates. The 4L LND+ group showed higher OS rates across all 5 years. Similarly, the 1–5-year DFS rates tended to be better in the 4L LND+ group. However, one study by Wang et al. reported contrary findings, showing that patients who did not undergo 4L lymph node dissection achieve better 1–5-year OS rates (7). Regarding the 1–5-year DFS rates, two studies made comparisons, and the results indicated that patients in the 4L LND+ group tended to have DFS rates over the 5-year period.



Both the postoperative hospital stay and the incidence of postoperative complications were similar between the two groups. Several factors may account for this finding. First, the similarity in hospital stay is likely due to the fact that 4L lymph node dissection does not significantly increase surgical trauma or impede postoperative recovery. The dissection itself is minimally disruptive to critical intrathoracic structures (e.g., aorta, thoracic ducts, etc.) when performed using standardized surgical techniques. Additionally, baseline characteristics (e.g., pulmonary function, surgical approach, anesthetic management, etc.) were likely comparable between the groups. Furthermore, standardized postoperative nursing care and rehabilitation protocols may have contributed to consistent hospitalization durations, regardless of whether 4L lymph node dissection was performed. The similarity in the incidence of postoperative complications is likely due to the fact that 4L lymph node dissection did not significantly increase the risk of intraoperative injuries (e.g., to the thoracic duct, aorta, or recurrent laryngeal nerve) when performed using standardized surgical techniques. Additionally, the anatomical structure of the left 4L region is relatively stable, and the dissection technique is well established. Moreover, preoperative evaluation, surgical scope, and perioperative management were likely comparable between the two groups, which may have contributed to the similar incidence of common complications such as infections, coeliac chest, or hemorrhage, regardless of whether 4L lymph node dissection was performed.

The discrepancies between our findings and previous studies may stem from differences in research design, sample characteristics, and methodological approaches. For instance, while Deng et al. focused on the Chinese population, our study enrolled a Polish population, which could influence outcomes due to ethic differences (23). Additionally, unlike studies that employed RCTs, our study included cohort studies, which may affect the credibility of the results. Variations in sample size (e.g., Deng et al.: n = 2,103 vs. our study: n = 4,253) may further account for the divergent results. These comparisons underscore the importance of contextualizing findings within study-specific parameters.

However, this study has several limitations. First, only five studies were included in the meta-analysis, which may affect its reliability and feasibility, even though all included studies were of high quality. Expanding the analysis to incorporate ongoing or recently completed RCTs or retrospective studies could offer a more comprehensive and up-to-date evaluation. Second, all studies included were published in English, which may introduce language bias. Future meta-analyses should consider incorporating studies published in multiple languages, potentially with professional translation support, to reduce selection bias. Third, since individual patient data could not be obtained, heterogeneity may exist among the included studies. Future research should aim to conduct individual patient data metaanalyses, which would enable a more personalized and precise assessment of treatment efficacy and safety. Fourth, the difference in OS between the two groups was not statistically significant, which may affect the overall conclusion. Additional studies are needed to enhance the reliability of the findings. Lastly, only two studies analyzed the DFS and 1-5-year DFS rates, which may also limit the reliability of the study. More research is required to strengthen the need to incorporate more research to improve.

Study or Subarous	4L LNI	D+ Total	4L LN	D- Total	Waight	Risk Ratio	Risk Ratio
	EVEIIIS	TULAI	EAGUI72	TULAI	TTCIGIIL	Modified by Eine	d offoata model
3.2.1 DSFR-19	040	445	404	404	E 40/		
wang 2018	340	415	121	134	5.4%	0.91 [0.84, 0.97]	-
W0 2022	321	416	329	416	9.7%	0.98 [0.91, 1.05]	-
Znao 2019 Subtotol (OER/ CI)	322	460	363	460	10.7%	0.89 [0.82, 0.96]	
Subtotal (95% CI)		1291		1010	23.7%	0.92 [0.86, 0.97]	•
I otal events	983	a (=	813				
Heterogeneity: Chi ² = 3 Test for overall effect: 2	3.55, df = Z = 3.48 (2 (P = P = 0.0	0.17); I² = 005)	= 44%			
3.2.2 DSFR-2y							
Wang 2018	266	415	105	134	6.8%	0.82 [0.73, 0.92]	
Wo 2022	277	416	273	416	7.5%	1.01 [0.92, 1.12]	+
Zhao 2019	276	460	299	460	7.4%	0.92 [0.83, 1.02]	
Subtotal (95% Cl)		1291		1010	21.6%	0.92 [0.81, 1.03]	•
Total events	819		677				
Heterogeneity: Tau² = (Test for overall effect: 2	0.01; Chi² Z = 1.40 (I	= 8.00, > = 0.16	df = 2 (P 3)	9 = 0.02); I² = 75%		
3.2.3 DSFR-3v							
Wang 2018	237	415	91	134	5.8%	0.84 [0 73 0 97]	
Wo 2022	207	416	235	416	6.7%	1 04 [0 92 1 17]	
7hao 2022	244	460	200	460	7 1%		
Subtotal (95% Cl)	200	1291	230	1010	19.6%	0.92 [0.81, 1.04]	•
Total events	734	1201	616		101070		•
Heterogeneity: Tau ² = (Test for overall effect: 2	0.01; Chi² Z = 1.35 (I	= 6.59, > = 0.18	df = 2 (P 3)	9 = 0.04); I² = 70%		
3.2.4 DSFR-4y							
Wang 2018	199	415	79	134	4.8%	0.81 [0.68, 0.97]	
Wo 2022	219	416	204	416	6.1%	1.07 [0.94, 1.23]	+
Zhao 2019	230	460	276	460	6.7%	0.83 [0.74, 0.94]	
Subtotal (95% CI)		1291		1010	17.6%	0.90 [0.76, 1.08]	\bullet
Total events	648		559				
Heterogeneity: Tau ² = (0.02; Chi ²	= 9.62,	df = 2 (P	= 0.00	8); l² = 79%	, 0	
Test for overall effect: 2	z = 1.14 (I	- = 0.2	5)		,,		
3.2.5 DSFR-5y							
	170	415	78	134	4.5%	0.70 [0.59, 0.85]	- -
Wang 2018	170		150	416	5.0%	1.20 [1.01, 1.42]	 -
Wang 2018 Wo 2022	180	416					
Wang 2018 Wo 2022 Zhao 2019	180 221	416 460	267	460	6.5%	0.83 [0.73, 0.94]	
Wang 2018 Wo 2022 Zhao 2019 Subtotal (95% Cl)	180 221	416 460 1291	267	460 1010	6.5% 1 6.0%	0.83 [0.73, 0.94] 0.89 [0.67, 1.18]	
Wang 2018 Wo 2022 Zhao 2019 Subtotal (95% CI) Total events	180 221 571	416 460 1291	267 495	460 1010	6.5% 16.0%	0.83 [0.73, 0.94] 0.89 [0.67, 1.18]	
Wang 2018 Wo 2022 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2	180 221 571 0.06; Chi ² Z = 0.81 (F	416 460 1291 = 19.93 P = 0.42	267 495 3, df = 2 (2)	460 1010 P < 0.0	6.5% 1 6.0% 001); I² = 9	0.83 [0.73, 0.94] 0.89 [0.67, 1.18] 0%	
Wang 2018 Wo 2022 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Total (95% CI)	180 221 571 D.06; Chi ² Z = 0.81 (I	416 460 1291 = 19.93 P = 0.42 6455	267 495 3, df = 2 (2)	460 1010 P < 0.0 5050	6.5% 16.0% 001); l² = 9 100.0%	0.83 [0.73, 0.94] 0.89 [0.67, 1.18] 0% 0.91 [0.86, 0.96]	•
Wang 2018 Wo 2022 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Total (95% CI) Total events	180 221 571 0.06; Chi ² Z = 0.81 (I 3755	416 460 1291 = 19.93 P = 0.42 6455	267 495 3, df = 2 (2) 3160	460 1010 P < 0.0 5050	6.5% 16.0% 001); I ² = 9 100.0%	0.83 [0.73, 0.94] 0.89 [0.67, 1.18] 0% 0.91 [0.86, 0.96]	•
Wang 2018 Wo 2022 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 7	180 221 571 0.06; Chi ² z = 0.81 (I 3755 0.01; Chi ² z = 3 43 (I	416 460 1291 = 19.93 P = 0.42 6455 = 48.40 P = 0.00	267 495 3, df = 2 (2) 3160 0, df = 14	460 1010 P < 0.0 5050 (P < 0.1	6.5% 16.0% 001); l ² = 9 100.0% 0001); l ² = ¹	0.83 [0.73, 0.94] 0.89 [0.67, 1.18] 0% 0.91 [0.86, 0.96] 71%	0.5 0.7 1 1.5 2
Wang 2018 Wo 2022 Zhao 2019 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for subcroup diffe	$180 \\ 221 \\ 571 \\ 0.06; Chi2 \\ z = 0.81 (I \\ 3755 \\ 0.01; Chi2 \\ z = 3.43 (I \\ z = 3.43 (I \\ z = 0.25; Cl) \\ z = 0.25; C$	416 460 1291 = 19.93 = 0.42 6455 = 48.40 P = 0.00 $hi^2 = 0.22$	267 495 3, df = 2 (2) 3160 0, df = 14 006)	460 1010 P < 0.0 5050 (P < 0.	6.5% 16.0% 001); l ² = 9 100.0% 0001); l ² = 0%	0.83 [0.73, 0.94] 0.89 [0.67, 1.18] 0% 0.91 [0.86, 0.96] 71%	• 0.5 0.7 1 1.5 2 Favours [4L LND+] Favours [4L LND+]

Conclusion

In summary, 4L LND+ appears to be a suitable choice for leftsided NSCLC, offering improved survival (OS and DFS) with similar rates of hospitalization, complications, and recurrence. The survival benefits associated with 4L LND+ increased over longer follow-up periods. However, due to the limitations mentioned above, these results require confirmation through additional large-sample randomized controlled trials (RCTs).

TABLE 2 Subgroup analysis of survival (OS and DFS) comparing 4L LND+ vs. 4L LND- in patients undergoing lobectomy.

Subgroups	No. of	Overall si	urvival	No. of	Disease-free survival						
	studies	HR (95% CI)	<i>p</i> -value	studies	HR (95% CI)	<i>p</i> -value					
Total	5	0.65 [0.52, 0.81]	< 0.0001	3	0.92 [0.66, 1.29]	0.64					
Published year	Published year										
Earlier than 2020	2	0.57 [0.52, 0.62]	< 0.00001	2	1.01 [0.87, 1.19]	0.86					
2020-2022	3	0.72 [0.60, 0.85]	< 0.0001	1	0.91 [0.75, 1.10]	0.34					
Nation											
China	5	0.60 [0.55, 0.65]	< 0.00001	3	0.97 [0.86, 1.10]	0.64					
Poland	-	_	-	-	-	-					
Follow-up time											
£60 month	2	0.72 [0.61, 0.86]	0.0003	1	1.25 [1.03, 1.52]	0.02					
> 60 month	3	0.57 [0.52, 0.62]	< 0.00001	2	0.82 [0.70, 0.96]	0.01					

OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval.

When the HR > 1, the results supported the 4L LND- group.

TABLE 3 Total adverse events according to the combination of two groups.

Adverse	Studies	4L LND+		4L LND-		Total	Risk	95%	<i>p</i> -value
effects	Involved	Event/ Total	%	Event/ Total	%	Incidence	ratio	CI	
Total	2	60/535	11.21%	51/609	8.37%	9.70%	1.45	1.01-2.08	0.04
Chylothorax	3	13/995	1.31%	11/1,069	1.03%	1.16%	1.28	0.58-2.84	0.54
Pneumonia	3	35/995	3.52%	28/1,069	2.62%	3.05%	1.29	0.79-2.10	0.31
Hemorrhage	2	8/535	1.50%	2/609	0.33%	0.87%	4.67	0.93- 23.46	0.06
Air leak > 7 days	1	10/416	2.40%	7/416	1.68%	2.04%	1.43	0.55-3.72	0.46
Chest tube drain > 7 days	2	65/876	7.42%	49/876	5.59%	6.51%	0.98	0.31-3.08	0.97
Heart failure	1	2/416	0.48%	2/416	0.48%	0.48%	1	0.14-7.07	1
Recurrent nerve injury	1	3/416	0.72%	1/416	0.24%	0.48%	3	0.31- 28.72	0.34
Hoarseness	1	5/460	1.09%	4/460	0.87%	0.98%	1.25	0.34-4.63	0.74
Bronchopleural fistula	2	5/579	0.86%	5/653	0.77%	0.81%	1.1	0.32-3.76	0.88
Deep venous thrombosis	1	1/460	0.22%	3/460	0.65%	0.43%	0.33	0.03-3.19	0.34
Pulmonary embolism	1	1/460	0.22%	1/460	0.22%	0.22%	1	0.06– 15.94	1
Arrhythmia	1	2/119	1.68%	3/193	1.55%	1.60%	1.08	0.18-6.38	0.93
Respiratory failure	1	2/119	1.68%	2/193	1.04%	1.28%	1.62	0.23- 11.36	0.63
Pneumothorax	1	7/119	5.88%	8/193	4.15%	4.81%	1.42	0.53-3.81	0.49
Incision infection	1	1/119	0.84%	0/193	0	0.32%	4.85	0.20- 118.09	0.33

(Continued)

TABLE 3 Continued

Adverse	Studies	4L LND+		4L LND-		Total	Risk	95%	<i>p</i> -value
effects	involved	Event/ Total	%	Event/ Total	%	incidence	ratio	CI	
Hydrothorax	1	1/119	0.84%	4/193	2.07%	1.60%	0.41	0.05-3.58	0.42
Others	1	4/119	3.36%	2/193	1.04%	1.92%	3.24	0.60– 17.44	0.17

4L, center lower paratracheal; LND, lymph node dissection; LND+, patients with lymph node dissection; LND-, patients without lymph node dissection; CI, confidence interval.

TABLE 4 Comparison of occurrence and distribution of mediastinal lymph node metastasis by LN station between LLL and LUL in the entire cohort.

Station	LN metastatic rate (%; involved/resected							
	Total	LUL	LLL					
L4	11.2 (57/510)	11.5 (39/338)	13.6 (18/132)					
5	15.9 (297/1,870)	20.6 (234/1,136)	8.6 (63/734)					
6	13.4 (122/911)	18.7 (99/530)	6 (23/381)					
7	11.5 (199/1,730)	4.4 (44/995)	21 (155/735)					
8	5.2 (12/233)	1.8 (2/113)	11.2 (10/89)					
9	6.1 (88/1,433)	1.7 (14/814)	11.9 (74/619)					
10	10.4 (24/230)	7.6 (11/145)	15.3 (13/85)					
11	13.9 (35/251)	7.7 (11/143)	22 (24/109)					
12	11.6 (25/215)	6.6 (8/122)	18.3 (17/93)					
13	11 (18/164)	7.4 (7/95)	15.9 (11/69)					

LUL, center upper lobe; LLL, center lower lobe.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

CL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. ZH: Conceptualization, Data curation, Formal Analysis, Writing – original draft. JW: Conceptualization, Data curation, Formal Analysis, Writing – original draft. WJZ: Conceptualization, Data curation, Formal Analysis, Writing – original draft. WXZ: Conceptualization, Data curation, Formal Analysis, Writing – original draft. CS: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2025.1583508/ full#supplementary-material

SUPPLEMENTARY FIGURE 1

Subgroup analysis of OSR (1–5 years) in LUL and LLL associated with 4L LND+ versus 4L LND- according to survival time.

SUPPLEMENTARY FIGURE 2

Comparison of postoperative hospital stay between the 4L LND+ and 4L LND- group.

SUPPLEMENTARY FIGURE 3 Forest plot of postoperative complications.

SUPPLEMENTARY FIGURE 4 Forest plot of recurrence.

SUPPLEMENTARY FIGURE 5 subgroup analysis of overall recurrence.

SUPPLEMENTARY FIGURE 6

Sensitivity analysis of OS and DFS.

SUPPLEMENTARY FIGURE 7 Publication bias of OS and DFS.

SUPPLEMENTARY TABLE 1 PRISMA 2009 Checklist.

SUPPLEMENTARY TABLE 2 Search strategy.

SUPPLEMENTARY TABLE 3 Methodological quality assessments of the included studies.

outcomes of survival and postoperative complications.

SUPPLEMENTARY TABLE 4 GRADE Quality assessment by therapeutic strategy and study design for the

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