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Neoadjuvant chemotherapy with or without PD-1/PD-L1 inhibitors in resectable esophageal squamous cell carcinoma: a meta-analysis based on randomized controlled trials

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Abstract

Background Neoadjuvant chemotherapy (NC) is a cornerstone in the management of resectable esophageal squamous cell carcinoma (ESCC). The integration of PD-1/PD-L1 inhibitors into NC (NIC) regimens has shown promise; however, its efficacy and safety remain uncertain. This meta-analysis aims to compare the potential risks and clinical benefits of NIC versus NC in patients with resectable ESCC based on randomized controlled trials (RCTs).

Methods A thorough search of six databases was performed to identify RCTs evaluating NIC and NC in resectable ESCC. Key outcomes analyzed included the pathological complete response (pCR) rate and the major pathological response (MPR) rate. Other outcomes analyzed included overall survival (OS), event-free survival (EFS), surgery rate, R0 resection rate, and adverse events (AEs).

Results Four RCTs encompassing 605 patients were included. NIC significantly improved pCR rate (risk ratio [RR]: 2.66 [1.63, 4.34], $P<0.0001$) and MPR rate (RR: 1.74 [1.02, 2.95], $P=0.04$) compared to the NC group. Only one phase III RCT reported survival outcomes, showing that the NIC group demonstrated improved OS (HR: 0.48 [0.24, 0.96], $P=0.04$) and EFS (HR: 0.62 [0.39, 0.99], $P=0.05$). Additionally, surgery rate (RR: 1.11 [1.03, 1.20], $P=0.008$) and the number of resected lymph nodes (mean difference [MD]: 3.91 [0.60, 7.21], $P=0.02$) were also higher in the NIC group. The R0 resection rate, duration of surgery, and intraoperative blood loss were comparable between the groups. However, the rate of immune-related AEs (irAEs) (RR: 40.80 [5.67, 293.37], $P=0.0002$) was significantly higher in the NIC group. Similar surgical complications were observed between the two groups.

Conclusions NIC demonstrates superior efficacy in improving pCR and MPR in resectable ESCC compared to NC alone, and may potentially provide survival benefits, although it is associated with a higher risk of irAEs.

Keywords Neoadjuvant, PD-1/PD-L1 inhibitors, Chemotherapy, Esophageal squamous cell carcinoma, Meta-analysis, Randomized controlled trials

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Introduction

Esophageal squamous cell carcinoma (ESCC) is a major global health burden, particularly prevalent in Asia, where it constitutes the predominant histological subtype of esophageal cancer [1]. Despite advances in surgical techniques and perioperative care, the prognosis for resectable ESCC remains poor [2]. Neoadjuvant chemotherapy (NC) has been established as the standard treatment for resectable ESCC, offering benefits such as tumor downstaging and improved R0 resection rates [3]. However, the pathological complete response (pCR) rates with NC alone are often suboptimal, and many patients still experience disease recurrence or progression [4]. This underscores the urgent need for more effective neoadjuvant strategies to improve long-term survival outcomes in ESCC patients.

In recent years, immune checkpoint inhibitors (ICIs), particularly PD-1/PD-L1 inhibitors, have emerged as transformative therapies for various cancers. ICIs function by restoring the immune system's capacity to identify and eliminate tumor cells, providing long-lasting responses in certain patients [5]. Combining PD-1/PD-L1 inhibitors with chemotherapy in the neoadjuvant setting (NIC) is a promising strategy, as chemotherapy-induced tumor cell death may enhance antigen release and synergize with ICIs to promote antitumor immunity [6]. Preliminary evidence from several phase II and III randomized controlled trials (RCTs) suggests that NIC increases pCR rates, improves major pathological response (MPR) rates, and potentially enhances overall survival (OS) in resectable ESCC [7–10]. However, this approach raises concerns regarding increased immune-related adverse events (irAEs) and the selection of appropriate patient subgroups who are most likely to benefit from this treatment [7, 8].

Despite encouraging early results, the integration of PD-1/PD-L1 inhibitors into neoadjuvant regimens for resectable ESCC remains controversial. Existing studies are limited in scale, and their results are often inconsistent, with some reporting significant survival benefits, while others fail to demonstrate substantial improvements in clinical outcomes [11, 12]. Furthermore, comprehensive evidence from RCTs assessing the safety and efficacy of this combination therapy is scarce, leaving clinicians with limited guidance on its optimal use [7–10]. This meta-analysis aims to address this knowledge gap by systematically reviewing and synthesizing data from RCTs comparing NIC with NC in resectable ESCC. By evaluating key endpoints such as pCR, MPR, OS, event-free survival (EFS), R0 resection rates, and adverse events (AEs), this study seeks to provide robust evidence to inform clinical decision-making and guide future research directions.

Materials and methods

Search strategy

The keywords used in the search strategy were "PD-1/PD-L1 inhibitors", "esophageal squamous cell carcinoma", and "randomized". Six databases, including PubMed, ScienceDirect, Cochrane Library, Scopus, EMBASE, and Web of Science, were thoroughly searched from their inception to December 15, 2024, as detailed in Table S1.

Selection criteria

Inclusion criteria (PICOS) were as follows:

(1) Participants (P): resectable ESCC.
(2) Intervention (I) and Control (C): NIC (PD-1/PD-L1 inhibitor [such as camrelizumab, toripalimab, or pembrolizumab, as described in the Table S1] in combination with platinum-based chemotherapy) versus NC (platinum-based chemotherapy). Treatment was administered for two to four cycles before surgery, depending on the specific trial protocol.
(3) Outcomes (O): Primary outcomes: pCR, and MPR; Secondary outcomes: survival (OS, and EFS), surgery rate, R0 resection rate, and AEs. OS was defined as the time from randomization to death from any cause. EFS was defined as the time from randomization to the occurrence of any event, including disease progression, recurrence, or death from any cause.
(4) Study design (S): RCTs.

The exclusion criteria included animal studies, meeting abstracts, review articles, meta-analyses, and case reports.

Data extraction

Two researchers independently collected details on study attributes (e.g., phase, duration), patient demographics (e.g., age, sex), survival outcomes (e.g., OS, EFS), pathological response rates (e.g., MPR, pCR), AEs, and other relevant information. For incomplete data, corresponding authors were contacted for clarification. Any disagreements were resolved through additional review.

Quality assessment

The included studies were assessed for quality using the Cochrane Risk of Bias Assessment Tool and the Jadad scale, a 5-point system where scores of ≥ 3 indicate high quality [13, 14]. To evaluate the reliability of

the findings, the GRADE approach was applied, categorizing the evidence into four levels: high, moderate, low, and very low [15].

Statistical analysis

Survival variables were analyzed using hazard ratios (HR), continuous variables using mean differences (MD), and dichotomous variables using risk ratios (RR). Survival rates for OS (OSR) and EFS (EFSR) were evaluated over a period of 3 to 24 months. A fixed-effects model was applied when $I^2 < 50\%$ or $P > 0.1$, indicating low heterogeneity; otherwise, a random-effects model was employed. Statistical significance was defined as *P* values less than 0.05. Publication bias was assessed through visual inspection of the funnel plot. Data analysis was conducted using Review Manager 5.3 and STATA 12.0. The study adhered to PRISMA guidelines and was registered with PROSPERO (ID: CRD42024634606).

Results

Search results

Among the 788 studies screened, 4 RCTs comprising 605 patients were ultimately included (Fig. 1). All included studies were assessed as high quality (Figure S1, Table S2). The baseline characteristics of these RCTs are summarized in Table 1. According to the GRADE approach, the quality of the evidence ranged from moderate to high (Table S3).

Pathological responses

The pCR rate was significantly higher in the NIC group (20.23% vs. 7.66%; RR: 2.66 [1.63, 4.34], $P < 0.0001$). Similarly, the MPR rate was also higher in the NIC group (39.69% vs. 23.40%; RR: 1.74 [1.02, 2.95], $P = 0.04$) (Fig. 2).

Survival

Only one phase III RCT (Zheng 2024 [10]) reported survival outcomes. In this study, the NIC group demonstrated improved OS (HR: 0.48 [0.24, 0.96], $P = 0.04$) and EFS (HR: 0.62 [0.39, 0.99], $P = 0.05$). Between 3 and 24 months, both OSR and EFSR favored NIC, with significant differences observed between 6 and 24 months for OSR (Figure S2) and between 6 and 18 months for EFSR (Figure S3).

Surgery rate

The NIC group achieved a higher surgery rate (RR: 1.11 [1.03, 1.20], $P = 0.008$). The R0 resection and reoperation rates were comparable between the two groups (Fig. 3).

Intraoperative and hospitalization indicators

A longer time from the last neoadjuvant dose to definitive surgery was observed in the NIC group (MD: 0.44 [0.17, 0.70] weeks, $P = 0.001$). In the surgical population, more lymph nodes were resected in the NIC group (MD: 3.91 [0.60, 7.21], $P = 0.02$) (Fig. 4). Similar durations of surgery, intraoperative blood loss, postoperative hospital stay, and postoperative drainage time were observed between the two groups (Figure S4).

Safety

In summary, the NIC group experienced more immune-related adverse events (irAEs) (RR: 40.80 [5.67, 293.37], $P = 0.0002$). The incidence of total AEs, grade 3–4 AEs, serious AEs, AEs leading to discontinuation, surgery delay or cancellation, death, treatment-related adverse events (TRAEs), grade 3–4 TRAEs, TRAEs leading to discontinuation or death, grade 3–4 irAEs, and surgical complications were comparable between the two groups (Table 2, Figure S5).

In the analysis of all-grade AEs, the NIC group showed higher incidences of anemia, decreased platelet count, hyponatremia, rash, hypothyroidism, reactive cutaneous capillary endothelial proliferation, and hyperthyroidism (Table S4). For grade 3–4 AEs, the NIC group had a higher incidence of decreased white blood cell count (Table S5). In the analysis of surgical complications, all complications were comparable between the two groups (Table S6).

Publication bias

The funnel plot symmetry for pathological responses, OSR, surgery rates, and the safety summary suggested an acceptable degree of publication bias (Fig. 5).

Discussion

While NC has been the standard for improving resection rates and downstaging tumors in resectable ESCC, its effectiveness in achieving optimal pathological responses and long-term survival outcomes remains limited [16]. PD-1/PD-L1 inhibitors have demonstrated significant efficacy in multiple cancers, including advanced ESCC, prompting their exploration in the neoadjuvant setting. Although the integration of PD-1/PD-L1 inhibitors into NC regimens has shown promise, its efficacy and safety remain uncertain, raising questions about their additive benefits, potential toxicity, and optimal patient selection [17]. This meta-analysis combined evidence from RCTs to evaluate the safety and efficacy of NIC versus NC. The findings indicate that NIC significantly improves key pathological and survival outcomes, such as pCR, MPR, OS, and EFS. However, these benefits are accompanied by a higher incidence of irAEs. These results highlight

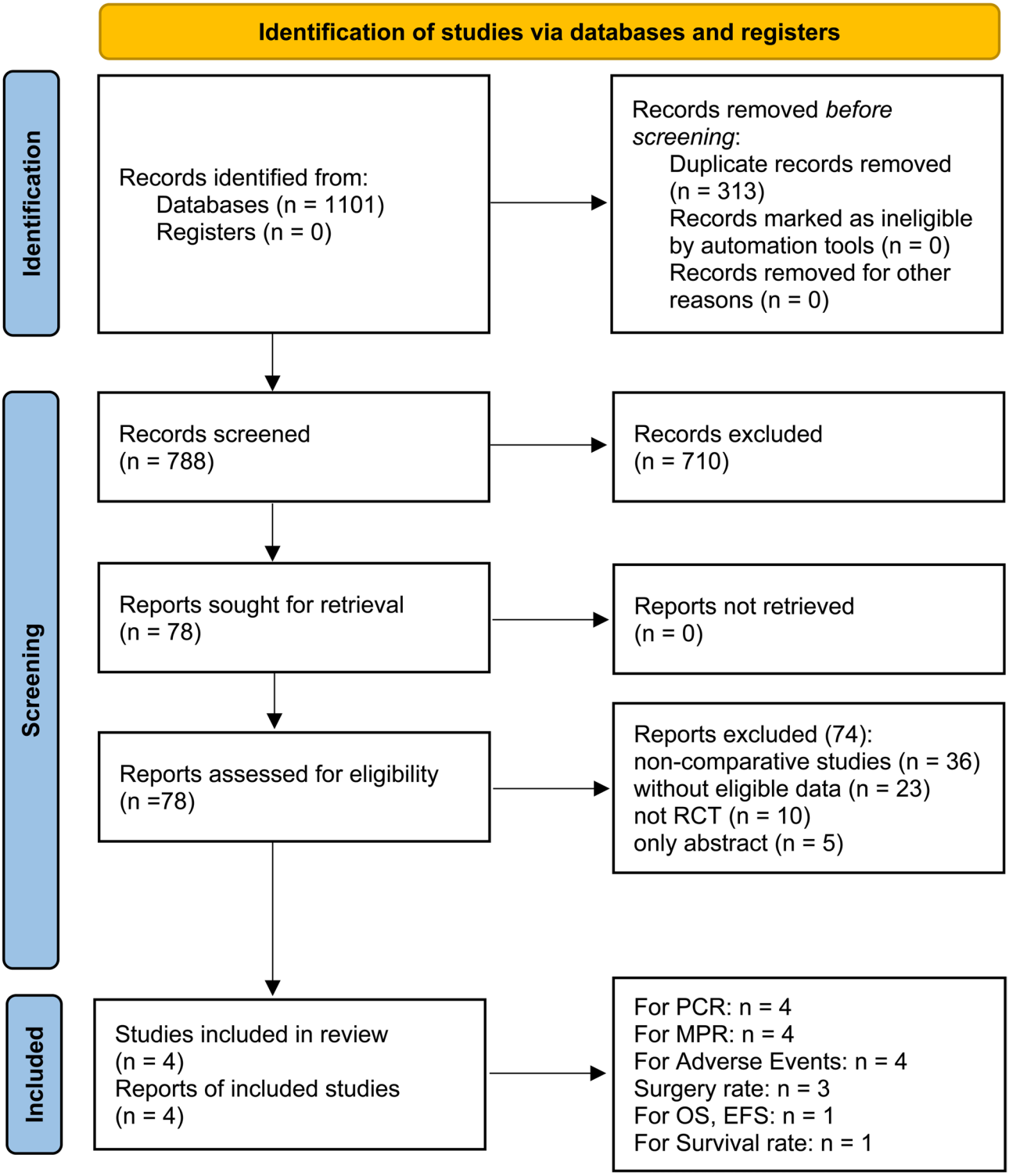

Fig. 1 Flow chart

the importance of balancing efficacy with safety while addressing critical questions regarding patient stratification, treatment timing, and optimal combination regimens.

The analysis revealed that NIC significantly enhances pCR (RR: 2.66) and MPR (RR: 1.74) rates compared to NC. These findings underscore the critical role of ICIs in augmenting the efficacy of chemotherapy. The observed improvements in pCR and

Table 1 Baseline characteristics of the included studies

Study	Phase	Period	Groups	Patients	Sex (M/F)	Age (Mean, year)	ECOG PS			Tumor location			Clinical stage				PD-1/PD-L1 type	Chemotherapy
							0	1	2	Upper	Middle	Lower	I	II	III	IVa		
Li 2024 [7]	2	2021.02-2021.07	NIC	32	23/9	61	25	7	0	9	18	5	0	5	26	1	Socazolimab	Nab-paclitaxel + Cisplatin
			NC	32	28/4	63	27	5	0	5	20	7	0	4	27	1		
Qin 2024 [8]	3	2021.04-2023.08	NIC	130	112/18	63	106	24	0	12	75	43	1	13	116	0	Camrelizumab	Paclitaxel + Cisplatin
			NC	129	104/25	65	104	25	0	19	57	53	2	19	108	0		
Wang 2023 [9]	2	2019.03-2021.04	NIC	15	13/2	61	15	0	0	1	11	3	0	3	6	6	Camrelizumab	Docetaxel + Cisplatin + Fluorouracil
			NC	15	15/0	63	15	0	0	1	13	1	0	1	11	3		
Zheng 2024 [10]	3	2020.05-2021.08	NIC	127	97/30	66	98	27	2	1	10	116	1	10	116	0	Toripalimab	Paclitaxel + Cisplatin
			NC	125	97/28	68	105	20	0	0	7	118	0	7	118	0		

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; M/F: Male/Female; NC: Neoadjuvant chemotherapy; NIC: Neoadjuvant chemotherapy with PD-1/PD-L1 inhibitors; PD-1: Programmed death-1; PD-L1: Programmed death-ligand 1

MPR rates are clinically significant, as pathological responses are strong predictors of long-term survival in ESCC patients undergoing neoadjuvant treatment. Previous studies have highlighted the importance of achieving pCR in reducing recurrence risk and improving survival outcomes. For example, Li et al. reported that a pCR rate exceeding 30% correlated with a 20% improvement in 3-year OS rates compared to patients without pCR [7]. Similarly, Qin et al. demonstrated that adding ICIs to NC regimens resulted in a 15% increase in MPR rates, emphasizing the synergistic effects of these agents [8]. Mechanistically, the integration of ICIs into neoadjuvant regimens leverages chemotherapy-induced immunogenic cell death, enhancing tumor antigen presentation and subsequent T-cell activation. This dual mechanism improves tumor eradication and establishes systemic immune surveillance, potentially reducing the likelihood of micrometastatic spread [18]. However, variability in pathological responses across studies underscores the need for better patient stratification. Biomarkers such as PD-L1 expression and tumor mutational burden (TMB) have shown promise in predicting responses to ICIs but require further validation in the neoadjuvant setting [19]. Future research should focus on developing predictive biomarkers to guide patient selection and optimize treatment outcomes. Additionally, the observed heterogeneity in pCR and MPR rates across studies may reflect differences in baseline characteristics of included populations. For instance, higher PD-L1 expression and elevated TMB have been associated with superior responses to ICIs in certain populations [20]. The interaction between these biomarkers and specific chemotherapy regimens may also contribute to variability. Understanding these interactions is essential for designing more effective NIC regimens and tailoring therapies to individual patients.

The survival benefits of NIC observed in our analysis are particularly noteworthy. NIC significantly improved OS (HR: 0.48) and EFS (HR: 0.62), with benefits extending up to 24 months post-treatment. These findings align with emerging evidence suggesting that the addition of ICIs to neoadjuvant regimens can induce durable antitumor immunity, thereby prolonging survival [21]. Notably, a recent phase III trial reported a 2-year OS rate of 78% with NIC compared to 60% with NC alone, further highlighting the transformative potential of this approach [10]. The observed improvement in EFS among NIC-treated patients suggests that this regimen not only delays disease progression but also reduces recurrence rates. The underlying mechanisms include enhanced T-cell activation, increased tumor antigen presentation, and improved immune memory. These results are

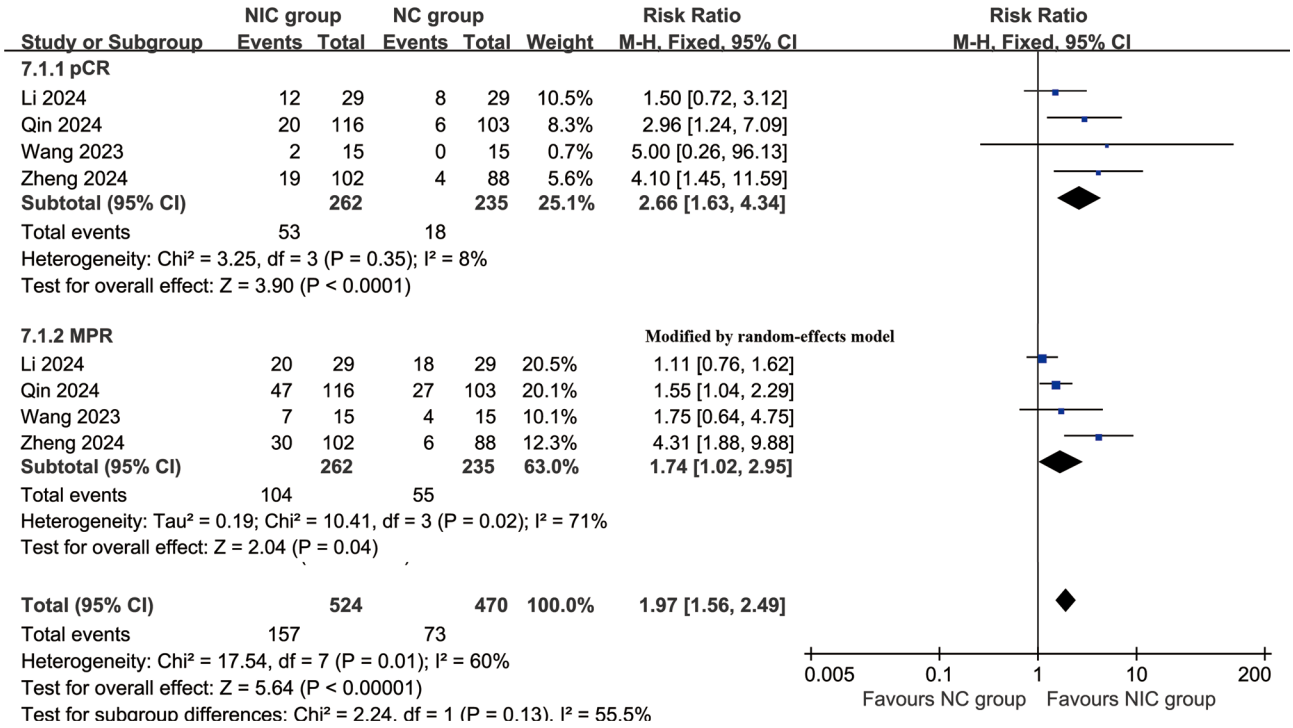

Fig. 2 Forest plots of pCR rates and MPR rates associated with NIC versus NC

consistent with findings by Zhang et al., who reported a 15% reduction in recurrence rates with NIC compared to NC alone [22]. However, several questions remain regarding the optimal duration and timing of NIC. Prolonged treatment courses may enhance efficacy but could also increase the risk of toxicity. Additionally, the role of consolidation or adjuvant ICIs following surgery remains an area of ongoing investigation [23]. Furthermore, survival benefits might be influenced by baseline tumor characteristics, such as stage, nodal involvement, and histological features. Recent studies have suggested that patients with earlier-stage disease or specific molecular subtypes, such as those with high immune infiltration, derive greater benefit from NIC [24]. Translating these findings into clinical practice will require the development of comprehensive risk stratification tools.

Our study demonstrated higher surgery rates and increased lymph node yield in the NIC group, indicating successful tumor downstaging. These findings are consistent with those of Wang et al., who reported a 10% increase in surgical eligibility among NIC-treated patients compared to those treated with NC [25]. The higher lymph node yield in the NIC group suggests improved nodal clearance, which has been associated with enhanced staging accuracy and a reduced risk of residual disease. Notably, similar R0 resection rates between the two groups indicate that the additional lymph node clearance did not compromise surgical margins [10]. Interestingly, the time from the last neoadjuvant dose to surgery was longer in the NIC group, potentially due to the need for recovery from irAEs. This delay underscores the importance of optimizing surgical timing to balance recovery and treatment efficacy. Despite this delay, other intraoperative indicators such as blood loss, operative time, and postoperative recovery parameters were comparable between the two groups, suggesting that NIC does not adversely affect surgical feasibility or outcomes [26, 27]. Another critical consideration is the potential impact of NIC on surgical complexity. While increased nodal clearance in NIC-treated patients may improve staging precision, it could also elevate operative difficulty in certain cases. These nuances emphasize the need for close collaboration between oncologists and surgeons to ensure optimal surgical outcomes.

While NIC demonstrated superior efficacy, it was associated with a significantly higher incidence of irAEs (RR: 40.80). Common irAEs included hypothyroidism, rash, and hematologic toxicities, consistent with the established toxicity profile of ICIs [28]. The overall safety profile of NIC aligns with findings from other studies in thoracic oncology. For example, Cheng et al. reported that although NIC increased irAEs, the rates of surgical complications, such as anastomotic leaks and infections, were comparable between groups [29]. This indicates that preoperative immune modulation does not compromise perioperative safety.

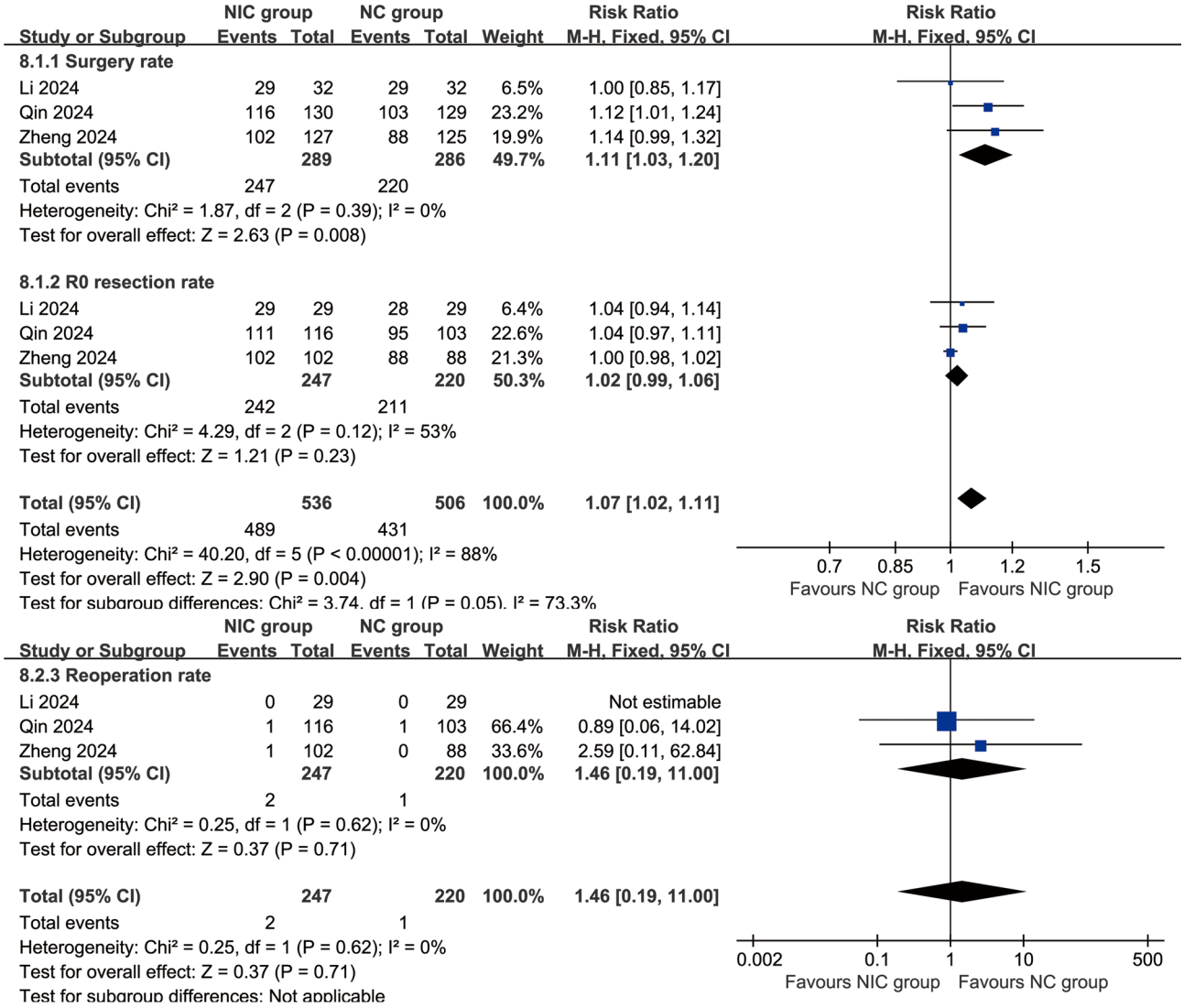

Fig. 3 Forest plots of surgery rate, R0 resection rate and reoperation rate associated with NIC versus NC

However, the impact of irAEs on treatment adherence and surgical timing warrants further investigation. Strategies such as steroid administration or temporary discontinuation of ICIs may help mitigate these risks without compromising efficacy [30]. Additionally, the long-term consequences of irAEs, including endocrine dysfunction and autoimmune disorders, remain insufficiently studied in NIC-treated populations. These concerns highlight the importance of multidisciplinary care teams capable of addressing both oncologic and immunologic challenges.

This study has several limitations that should be acknowledged. First, the small number of included RCTs and the relatively limited sample size ($n = 605$) restrict the generalizability of our findings. Second, heterogeneity in study designs, including variations in chemotherapy regimens, ICI agents, quality of surgical procedures, and outcome definitions, may have introduced bias. Third, the lack of individual patient data precluded detailed subgroup analyses, which could have identified predictors of benefit. Fourth, the short follow-up durations of the included studies limit the ability to assess long-term outcomes, such as 5-year survival rates. Fifth, only one small sample phase II trial (Zheng 2024 [10]) provided survival data, limiting the strength of conclusions regarding long-term outcomes. Finally, while publication bias appeared minimal, it cannot be entirely excluded. Future research should address these limitations by conducting larger, multicenter trials with standardized protocols and longer follow-up periods.

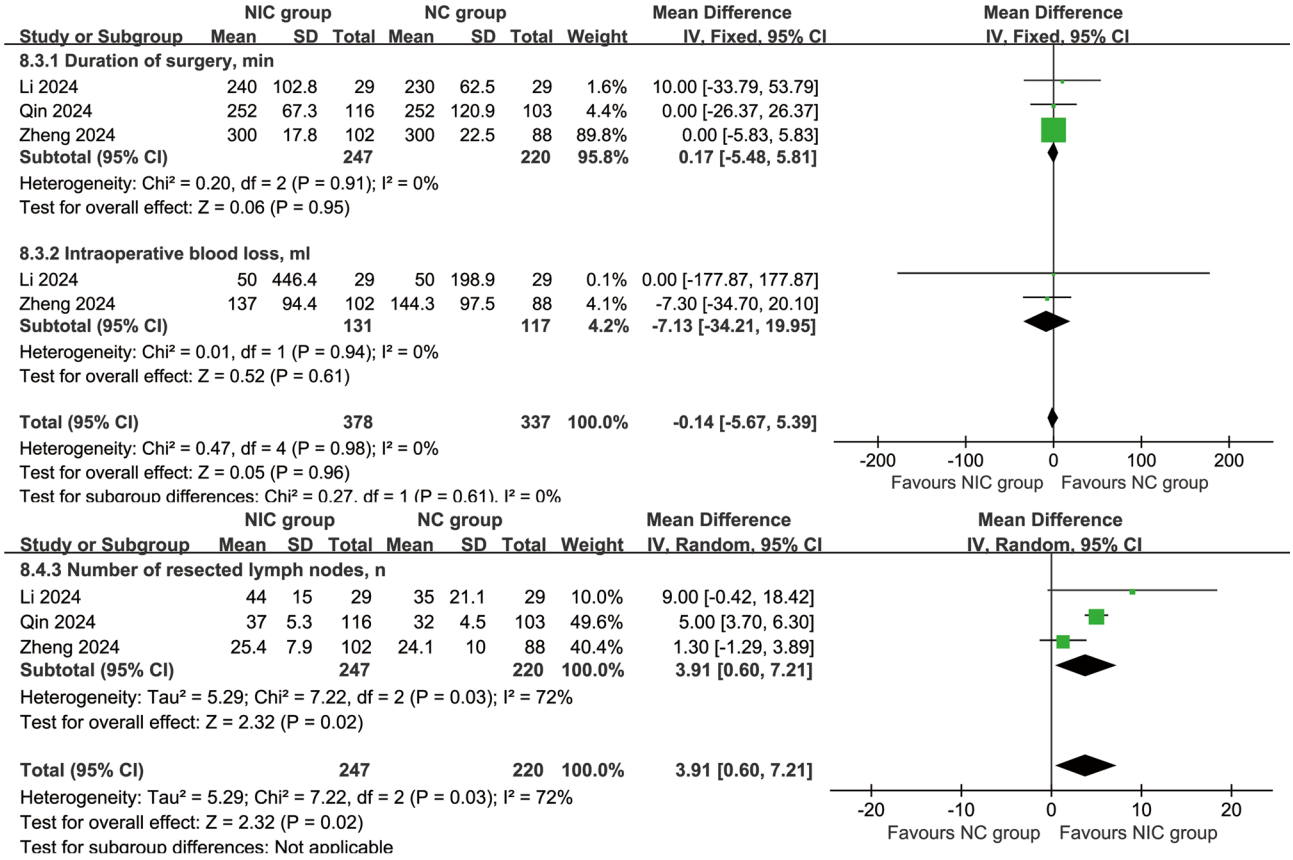

Fig. 4 Forest plots of intraoperative indicators associated with NIC versus NC

Table 2 Summary of adverse events

Adverse events	NIC		NC		Risk ratio [95% CI]	*P*
	Event/total	%	Event/total	%		
Total AEs	270/289	93.43%	265/286	92.66%	1.00 [0.92, 1.09]	0.98
Grade 3–4 AEs	95/304	31.25%	99/301	32.89%	0.95 [0.76, 1.19]	0.67
Serious AEs	43/289	14.88%	34/286	11.89%	1.25 [0.83, 1.89]	0.29
AEs leading to discontinuation	8/289	2.77%	6/286	2.10%	1.31 [0.15, 11.91]	0.81
AEs leading to surgery delay/cancellation	2/159	1.26%	1/157	0.64%	1.65 [0.22, 12.32]	0.62
AEs leading to death	1/162	0.62%	0/161	0.00%	2.98 [0.12, 72.41]	0.50
TRAEs	260/289	89.97%	261/286	91.26%	0.99 [0.94, 1.04]	0.59
Grade 3–4 TRAEs	74/289	25.61%	72/286	25.17%	1.02 [0.79, 1.33]	0.88
TRAEs leading to discontinuation	7/289	2.42%	5/286	1.75%	1.35 [0.45, 4.02]	0.59
TRAEs leading to death	1/162	0.62%	0/161	0.00%	2.98 [0.12, 72.41]	0.50
irAEs	40/162	24.69%	0/161	0.00%	40.80 [5.67, 293.37]	0.0002
Grade 3–4 irAEs	6/162	3.70%	0/161	0.00%	6.97 [0.87, 56.03]	0.07

Abbreviations: AE: Adverse event; CI: Confidence interval; irAE: Immune-related adverse event; NC: Neoadjuvant chemotherapy; NIC: Neoadjuvant chemotherapy with PD-1/PD-L1 inhibitors; RR: Risk ratio; TRAE: Treatment-related adverse event

Conclusions

NIC significantly improves pCR and MPR in resectable ESCC and may potentially offer survival benefits. However, the increased risk of irAEs associated with NIC underscores the importance of careful patient selection and management. Future studies should prioritize refining biomarkers for patient stratification, optimizing treatment protocols, and investigating the long-term benefits of NIC. Addressing these challenges will be critical to advancing neoadjuvant strategies and improving the prognosis for patients with resectable ESCC.

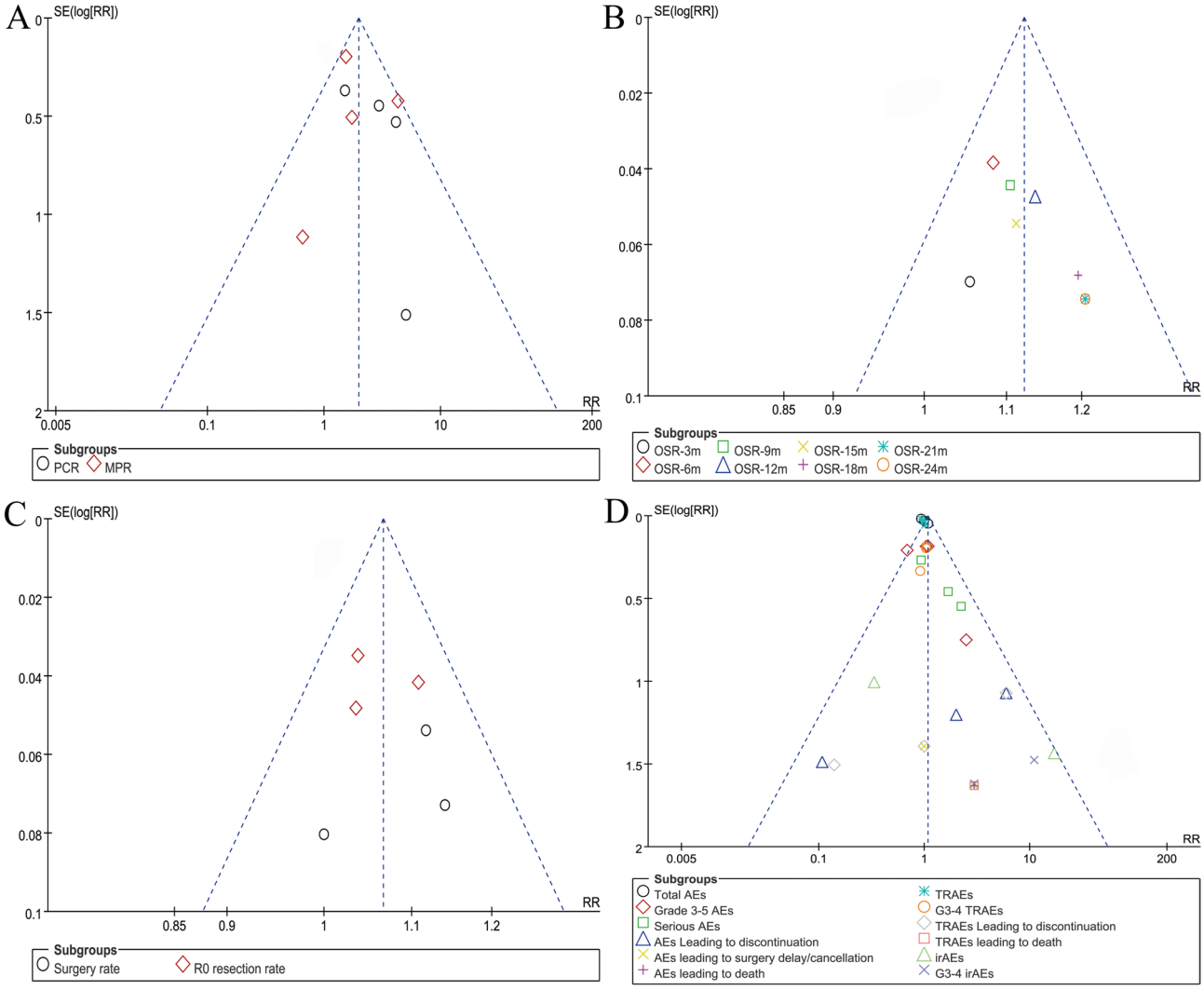

Fig. 5 Funnel plots of pathological responses (**A**), OSR (**B**), surgery rates (**C**), and safety summary (**D**)

Abbreviations

AE	Adverse event
CI	Confidence interval
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EFS	Event-free survival
EFSR	Event-free survival rate
ESCC	Esophageal squamous cell carcinoma
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratio
ICI	Immune checkpoint inhibitor
irAE	Immune-related adverse event
MD	Mean difference
M/F	Male/Female
MPR	Major pathological response
NC	Neoadjuvant chemotherapy
NIC	Neoadjuvant chemotherapy with PD-1/PD-L1 inhibitors
OS	Overall survival
OSR	Overall survival rate
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
pCR	Pathological complete response
PICOS	Participants, Interventions, Comparators, Outcomes, Study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomized controlled trial
RR	Risk ratio
TMB	Tumor mutational burden
TRAE	Treatment-related adverse event

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

Supplementary Material 11

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Author contributions
Yingmei Zhong had full access to all of the data in the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Ye Zhang, Jie Chen, Fenglian Yu, Wenxiong Zhang, and Yingmei Zhong. Acquisition, analysis, or interpretation of data: Ye Zhang, Jie Chen, Fenglian Yu, Wenxiong Zhang, and Yingmei Zhong. Drafting of the manuscript: Ye Zhang, and Yingmei Zhong. Critical revision of the manuscript for important intellectual content: Ye Zhang, and Yingmei Zhong. Statistical analysis: Ye Zhang, and Yingmei Zhong. Supervision: Ye Zhang, and Yingmei Zhong.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
As a systematic review and meta-analysis, our study did not require any human participation and, referral to our ethics committee.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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