Supplemental Online Content

Ge F, Huo Z, Cai X, et al. Evaluation of clinical and safety outcomes of neoadjuvant immunotherapy combined with chemotherapy for patients with resectable esophageal cancer: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(11):e2239778. doi:10.1001/jamanetworkopen.2022.39778

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Inclusion and Exclusion Criteria.	
Inclusion Criteria	Exclusion Criteria
1. Published as full-length articles in English	1. Studies reporting inoperable, or metastatic disease
2. Phase II/III clinical trials reporting resectable stage I-IV esophageal cancer (including ESCC and EAC) confirmed by tissue	2. Included patients had received prior immunotherapy or chemoradiotherapy
3. Studies that included patients who received ICIs preoperatively as monotherapy or in combination with other therapies (including chemotherapy, and chemoradiotherapy)	3. Phase I clinical trials or real-world studies
4. Studies reporting the complete protocol, recruited patient data and at least one primary or secondary clinical outcome, such as pCR rate, MPR rate, ORR, DCR, the incidence of side effects were more than grade 3 tr-SAE, R0 surgical resection rate, and the incidence of surgical complications	4. Studies reporting invalid data for the efficacy and safety of neoadjuvant immunotherapy
	5. Studies that violated any of the inclusion criteria above. The reviewers further exclude case reports, systematic reviews or meta- analyses, and cell culture or animal studies, but not conference summaries
	rcinoma; ICI, immune checkpoint inhibitor; pCR, pathological complete rate; DCR, disease control rate; tr-SAE, treatment-related severe adverse

eTable 2. Meth	nodologica	al quality a	assessmen	t of includ	ed studies:	MINORS	5					
Study	1	2	3	4	5	6	7	8	9*	11*	12*	Score [#]
Lee et al, ²¹ 2019	2	2	1	2	2	2	2	2	NA	NA	NA	15
van den Ende et al, ²² 2019	2	2	2	1	2	2	2	1	NA	NA	NA	14
Gu et al, ²³ 2020	2	2	2	2	2	2	2	1	NA	NA	NA	15
Zhang et al, ²⁵ 2020	2	2	1	2	2	2	2	2	NA	NA	NA	15
Park et al, ²⁴ 2020	2	2	1	1	2	1	2	1	NA	NA	NA	12
Zhang et al, ⁴⁰ 2021	2	2	1	2	2	2	2	2	NA	NA	NA	15
Duan et al, ²⁷ 2021	2	2	1	2	2	2	2	2	NA	NA	NA	15
Xing et al, ²⁸ 2021	2	2	1	2	2	2	2	1	2	2	2	23
Huang et al, ²⁹ 2021	2	2	1	1	2	2	2	1	2	2	2	22
Wu et al, ³⁷ 2021	2	2	2	1	2	2	2	1	NA	NA	NA	14
He et al, ⁴² 2021	2	2	1	2	2	2	2	2	NA	NA	NA	15
Ma et al, ³² 2021	2	2	2	2	2	2	2	1	NA	NA	NA	15
Yan et al, ³⁸ 2021	2	2	2	2	2	2	2	1	NA	NA	NA	15
Wang et al, ³⁵ 2021	2	2	2	2	2	2	2	2	NA	NA	NA	16
Zhang et al, ⁴¹ 2021	2	2	2	2	2	2	2	1	NA	NA	NA	15

Wang et al, ³⁶	2	2	2	2	2	2	2	1	NA	NA	NA	15
2021												
Li et al, ³⁰	2	2	1	2	2	2	2	2	NA	NA	NA	15
2021												
Liu et al, ³¹ 2021	2	2	1	2	2	2	2	1	NA	NA	NA	14
Yang et al, ⁴⁷ 2021	2	2	1	2	2	2	2	2	NA	NA	NA	15
Shang et al, ³³ 2021	2	2	1	2	2	2	2	1	NA	NA	NA	14
Liu et al, ⁴³ 2021	2	2	2	2	2	2	2	1	NA	NA	NA	15
Shen et al, ³⁴ 2021	2	2	1	2	2	2	2	2	NA	NA	NA	15
Yang et al, ³⁹ 2021	2	2	1	2	2	2	2	1	NA	NA	NA	14
Athauda et al, ²⁶ 2021	2	2	1	1	2	2	2	1	NA	NA	NA	13
Sun et al, ⁴⁵ 2022	2	2	1	2	2	2	2	1	NA	NA	NA	14
Liu et al, ⁴⁴ 2022	2	2	1	2	2	2	2	2	NA	NA	NA	15
Xu et al, ⁴⁶ 2022	2	2	2	2	2	2	2	1	NA	NA	NA	15
*, For compara	tive studie	es only.										

#, Scores of at least 75% were considered high quality with low risk for bias; scores between 50% and 75% were considered medium risk for bias; scores of less than or equal to 50% were considered high risk for bias. For noncomparative studies, the maximum score was 16, while the maximum score for comparative studies was 24. MINORS, Methodological index for non-randomized studies

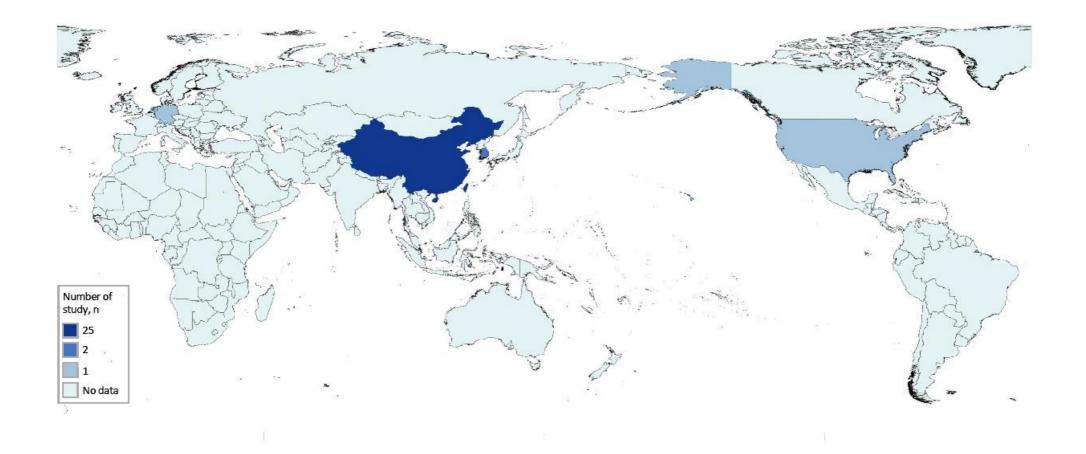
Attachment: MINORS Evaluation Criteria	
Methodological items for non-randomized studies	Score [#]
1. A clearly stated aim: the question addressed should be precise and relevant in the light of available literature	
2. Inclusion of consecutive patients: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been	
included in the study during the study period (no exclusion or details about the reasons for exclusion)	
3. Prospective collection of data : data were collected according to a protocol established before the beginning of the study	
4. Endpoints appropriate to the aim of the study: unambiguous explanation of the criteria used to evaluate the main	
outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on	
an intention-to-treat basis.	
5. Unbiased assessment of the study endpoint: blind evaluation of objective endpoints and double-blind evaluation of	
subjective endpoints. Otherwise the reasons for not blinding should be stated	
6. Follow-up period appropriate to the aim of the study: the follow-up should be sufficiently long to allow the assessment	
of the main endpoint and possible adverse events	
7. Loss to follow up less than 5%: all patients should be included in the follow up. Otherwise, the proportion lost to follow	
up should not exceed the proportion experiencing the major endpoint	
8. Prospective calculation of the study size: information of the size of detectable difference of interest with a calculation of	
95% confidence interval, according to the expected incidence of the outcome event, and information about the level for	
statistical significance and estimates of power when comparing the outcomes	
Additional criteria in the case of comparative study	
9. An adequate control group: having a gold standard diagnostic test or therapeutic intervention recognized as the optimal	
intervention according to the available published data	
10. Contemporary groups: control and studied group should be managed during the same time period (no historical	
comparison)	
11. Baseline equivalence of groups : the groups should be similar regarding the criteria other than the studied endpoints.	
Absence of confounding factors that could bias the interpretation of the results	
12. Adequate statistical analyses: whether the statistics were in accordance with the type of study with calculation of	
confidence intervals or relative risk	
# The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being	16 for
non-comparative studies and 24 for comparative studies.	

eTable 3	. Su	mmary of surg	gical complic	ations in i	ncluded studies										
	N	Overall surgical complicati on, N (%)	Pneumoni a, N (%)	Pleural effusio n, N (%)	Pneumothor ax, N (%)	Chylothora x, N (%)	ARDS , N (%)	Respirato ry failure, N (%)	Heart failure , N (%)	Anastomot ic fistula, N (%)	Hoars e voice, N (%)	Bleedin g, N (%)	Wound infectio n, N (%)	ICU treatme nt, N (%)	Die, N (%)
Lee et al, ²¹ 2019	2 6	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Zhang et al, ⁴⁰ 2021	2 3	-	15 (65.2%)	10 (43.5%)	-	1 (4.3%)	-	-	-	3 (13.0%)	1 (4.3%)	1 (4.3%)	-	-	-
Duan et al, ²⁷ 2021	1 7	-	6 (35.2%)	-	-	-	2 (11.8 %)	2 (11.8%)	4 (23.5 %)	2 (11.8%)	5 (29.4 %)	-	-	-	-
Xing et al, ²⁸ 2021	1 1	-	5 (45.5%)	-	-	-	-	-	-	1 (9.1%)	-	-	-	-	-
Huang et al, ²⁹ 2021	2 1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Wu et al, ³⁷ 2021	3 8	10 (26.3%)	9 (23.7%)	-	-	1 (2.9%)	-	-	-	-	-	-	1 (2.9%)	5 (14.3%)	-
He et al, ⁴² 2021	1 6	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gu et al, ²³ 2020	1 5	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ma et al, ³² 2021	7	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Yan et al, ³⁸ 2021	3 6	-	-	-	-	-	-	-	-	-	-	-	-	-	-

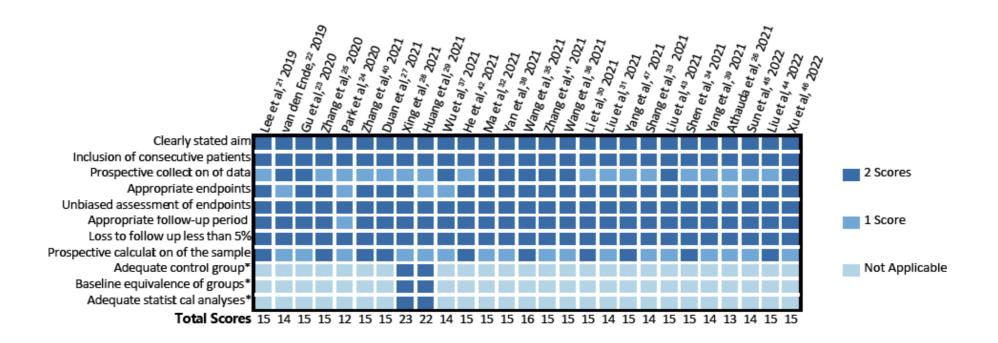
		1			1	1				1		1		1	
Sun et	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-
al, ⁴⁵	6														
2022															
Wang	1	-	-	-	-	-	-	-	-	-	-	-	_	_	-
et al, 35	2														
2021	4														
Liu et	5	24	5	3	2	4			2		13			1	
						4	-	-	2	-		-	-	1	-
al, ⁴⁴	1	(47.1%)	9.8%	5.9%	(3.9%)	(7.8%)			(3.9%)		(25.5			(2.0%)	
2022											%)				
Zhang	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-
et al,41	0														
2021															
Xu et	4	-	-	-	-	-	-	-	-	-	-	-	_	-	-
al, ⁴⁶	6														
2022	Ŭ														
Wang	2	-	-	_	_	_	_	-	_	-	_	-	-	-	-
wang		-	-	-	-	-	-	-	-	-	-	-	-	-	-
et al, ³⁶	4														
2021															
Liu et	2	-	-	-	-	-	-	-	-	1	-	-	-	-	-
al, ³¹	8									(3.6%)					
2021															
Liu et	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
al, ³¹	8														
2021	-														
van	3	-	10	-	_	5	_	_	_	7	_	-	-	_	-
den	3		(30.3%)	_	_	(15.2%)	_		-	(21.2%)	_	_	_	_	
Ende	5		(30.370)			(13.270)				(21.270)					
et al, ²²															
2019															
Yang	2	-	-	-	-	-	-	-	-	2	1	1	1	-	-
et al, ⁴⁷	0									(10.0%)	(5.0%)	(5.0%)	(5.0%)		
2021															
	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Zhang et al, ²⁵	8														
2020	Ŭ														
2020							L		L		L		L	L	

Shang et al, ³³ 2021	2 9	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Liu et al, ⁴³ 2021	5 1	14 (27.5%)	7 (13.7%)	3 (5.9%)	2 (3.9%)	-	-	-	-	3 (5.9%)	5 (9.8%)	-	1 (2.0%)	-	-
Park et al, ²⁴ 2020	1 6	11 (68.8%)	-	-	-	-	3 (18.8 %)	3 (18.8%)	-	3 (18.8%)	3 (18.8 %)	-	1 (6.3%)	-	2 (12. 5)
Shen et al, ³⁴ 2021	2 7	-	3 (11.1%)	4 (14.8%)	-	2 (7.4%)	-	-	-	5 (18.5%)	2 (7.4%)	-	-	-	-
Yang et al, ³⁹ 2021	1 2	2 (16.7%)	-	-	-	-	-	-	-	2 (16.7%)	-	-	-	-	-
Athau da et al, ²⁶ 2021	1 5	5 (33.3%)	-	-	-	-	-	-	-	1 (6.7%)	-	-	-	-	-
	er; A	ARDS, acute re	espiratory dis	stress synd	lrome; ICU, inte	ensive care un	it				1				I

eFigure 1. The geographical distribution of included studies. Color depth is proportional to the number of included studies, including 22 in China, 2 in South Korea, 1 in Germany, 1 in the Netherlands, and 1 in the USA.



eFigure 2. Methodological quality assessment of included studies. *, For comparative studies only. #, Scores of at least 75% were considered high quality with low risk for bias; scores between 50% and 75% were considered medium risk for bias; scores of less than or equal to 50% were considered high risk for bias. For noncomparative studies, the maximum score was 16, while the maximum score for comparative studies was 24.



eFigure 3. Forest plot of the primary outcomes for efficacy in neoadjuvant immunotherapy combined with chemotherapy in ESCC stratified by ICI types. (A)

the pCR rate, (B) the MPR rate. CI, confidence interval; ESCC, esophageal squamous cell carcinoma; ICI, immune-checkpoint inhibitors; pCR, pathological

Α				В							
Study Events Total	Proportion 95	Weight 5%-CI (common)	Weight (random)	Study	Events	Total		Proportion	95%-CI	Weight (common)	Weight (random)
Drug = Pembrolizumab											
Lee et al, 21 2019 12 26	0.462 [0.266;	0.666] 4.9%	5.0%	Drug = Sintilimab			i				
Shang et al, 33 2021 12 29	0.414 [0.235;		5.5%	Zhang et al, 40 2021	12	23		0.522	[0.306; 0.732]	5.6%	6.2%
Common effect model 55	0.436 [0.305;			Duan et al, 27 2021	9	17		0.529	[0.278; 0.770]	4.1%	5.2%
Random effects model	0.436 [0.305;	0.572]	10.5%	Gu et al, 23 2020	8	15		0.533	[0.266; 0.787]	3.7%	4.9%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.73$				Zhang et al, 41 2021	19	40		0.475	[0.315; 0.639]	9.6%	7.8%
Deug - Cintilianala				Common effect model		95		0.505	[0.402; 0.609]	22.9%	
Drug = Sintilimab Zhang et al, ⁴⁰ 2021 5 23	0.217 [0.075;	0.437] 4.4%	4.4%	Random effects model				0.505	[0.402; 0.609]		24.1%
Duan et al, ²⁷ 2021 6 17	0.353 [0.142;		3.3%	Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0. p = 0.97				L		
Gu et al, ²³ 2020 4 15	0.267 [0.078;		3.0%								
Zhang et al, 41 2021 10 40	0.250 [0.127;		7.4%	Drug = Multiple			1				
Common effect model 95	0.261 [0.173;	0.357] 18.0%		Wu et al, 37 2021	16	38		0.421	[0.263; 0.592]	9.1%	7.7%
Random effects model	0.261 [0.173;	0.357]	18.1%	Shen et al, ³⁴ 2021	10	27		0.421		6.5%	6.7%
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.82$					11	65			[0.224; 0.612]		0.7%
				Common effect model		60		0.415	[0.296; 0.539]	15.6%	
Drug = Toripalimab				Random effects model				0.415	[0.296; 0.539]		14.3%
Xing et al, ²² 2021 4 11 He et al, ⁴² 2021 3 16	0.364 [0.109;		2.2% 3.1%	Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0\%$	0, p = 0.92		i				
He et al, ⁴² 2021 3 16	0.188 [0.040; 0.333 [0.133;		3.1%								
Zhang et al, ²⁵ 2020 3 18	0.333 [0.133; 0.167 [0.036;		3.5%	Drug = Toripalimab			:				
Common effect model 63	0.249 [0.144; (3.378	He et al, 42 2021	7	16		0.438	[0.198; 0.701]	3.9%	5.1%
Random effects model	0.249 [0.144; (12.4%	Zhang et al, 25 2020	9	18		0.500	[0.260; 0.740]	4.4%	5.4%
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.53$	- b' /			Common effect model		34		0.471	[0.301; 0.644]	8.3%	
				Random effects model				0.471	[0.301; 0.644]		10.5%
Drug = Multiple				Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$	0, <i>p</i> = 0.73						
Wu et al, 37 2021 13 38	0.342 [0.196;		7.1%				1				
Shen et al, ³⁴ 2021 9 27	0.333 [0.165;		5.1%	Drug = Tislelizumab			1				
Common effect model 65	0.338 [0.226; 0 0.338 [0.226; 0		12.2%	Yan et al, 38 2021	26	36	· · · · · · · · · · · · · · · · · · ·	0.722	[0.548; 0.858]	8.6%	7.5%
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.95$	0.336 [0.226,0	0.460]	12.270								
That of og of holds () = 0.0, (= 0, p = 0.00				Drug = Camrelizumab			i				
Drug = Camrelizumab				Wang et al, 35 2021	5	12		0.417	[0.152; 0.723]	3.0%	4.2%
Ma et al, 32 2021 4 7	0.571 [0.184;	0.901] 1.4%	1.5%	Xu et al, ⁴⁶ 2022	18	37		0.486	[0.319; 0.656]	8.9%	7.6%
Wang et al, 35 2021 3 12	0.250 [0.055;		2.4%	Wang et al, ³⁶ 2021	14	24		0.583	[0.366; 0.779]	5.8%	6.3%
Liu et al, 44 2022 20 51	0.392 [0.258;		9.2%	Yang et al, 47 2021	10	20		0.500	[0.272; 0.728]	4.8%	5.7%
Xu et al, ⁴⁶ 2022 8 37 Wang et al, ³⁶ 2021 7 24	0.216 [0.098;		6.9%	Liu et al, 43 2021	12	51		0.235	[0.128; 0.375]	12.2%	8.5%
Wang et al, ³⁶ 2021 7 24 Yang et al, ⁴⁷ 2021 5 20	0.292 [0.126; 0.250 [0.087;		4.6% 3.9%	Yang et al, 39 2021	5	12		0.200	[0.152; 0.723]	3.0%	4.2%
Liu et al, 43 2021 18 51	0.353 [0.224;		9.2%	Common effect model	5	156		0.405	[0.326; 0.486]	37.6%	4.270
Yang et al, ³⁹ 2021 4 12	0.333 [0.099;		2.4%	Random effects model		150					36.7%
Common effect model 214	0.317 [0.253; 0				0.0115	0.05		0.427	[0.306; 0.553]		30.770
Random effects model	0.317 [0.253;	0.384]	40.1%	Heterogeneity: $I^2 = 56\%$, $\tau^2 =$: 0.0115, p :	= 0.05	i				
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.58$:				
				Drug = Pembrolizumab			:				
Drug = Tislelizumab	0.500 10.000	0.0741 0.004	0.70/	Shang et al, 33 2021	21	29		0.724	[0.528; 0.873]	7.0%	6.9%
Yan et al, 38 2021 18 36	0.500 [0.329;	0.671] 6.8%	6.7%	0		445	1	0.400	TO 400. 0 FOOT	400.001	
Common effect model 528	0.325 [0.284;	0.367] 100.0%		Common effect model		415		0.486	[0.436; 0.536]	100.0%	
Random effects model	0.324 [0.282;		100.0%	Random effects model				0.494	[0.421; 0.567]		100.0%
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0.0005$, $p = 0.51$ 0,2 0,4 0,6 0,6				Heterogeneity: $I^2 = 53\%$, $\tau^2 =$	= 0.0102, p •	< 0.01	0.2 0.3 0.4 0.5 0.6 0.7 0.8				
Test for subgroup differences (fixed effect): $\chi_5^2 = 10.19$, df = 5(p = 0.07)				Test for subgroup differences	(fixed effec	t): $\chi_5^2 = 20.16$					
Test for subgroup differences (random effects): $\chi_5^2 = 10.19$, df = 5($p = 0.07$)				Test for subgroup differences	(random ef	fects): $\chi_5^2 = 1$	16.24, df = 5(<i>p</i> < 0.01)				

complete response; MPR, major pathological response

eFigure 4. Forest plot of the secondary outcomes for efficacy in neoadjuvant immunotherapy combined with chemotherapy in ESCC stratified by ICI types. (A) CR, (B) PR, (C) SD, (D) ORR, (E) DCR. CI, confidence interval; ESCC, esophageal squamous cell carcinoma; ICI, immune-checkpoint inhibitors; PR, partial response; CR, complete response; SD, stable disease; ORR, objective response rate; DCR, disease control rate

A						Weight	Weight
Study	Events	Total		Proportion	95%-CI	(common)	(random)
Drug = Sintilimab			i i				
Duan et al, 27 2021	3	8		0.375	[0.085; 0.755]	4.9%	10.1%
Drug = Pembrolizumab							
Huang et al, 29 2021	8	23		0.348	[0.164; 0.573]	13.5%	14.7%
Drug = Toripalimab							
He et al, ⁴² 2021	6	18		0.333	[0.133; 0.590]	10.6%	13.7%
Drug = Camrelizumab							
Ma et al, 32 2021	1	21		0.048	[0.001; 0.238]	12.3%	14.4%
Yang et al, 47 2021	1	23		0.043	[0.001; 0.219]	13.5%	14.79
Liu et al, 43 2021	7	51		0.137	[0.057; 0.263]	29.5%	17.19
Common effect model		95		0.089	[0.036; 0.159]	55.3%	_
Random effects model			-	0.088	[0.033; 0.161]		46.2%
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0.0005, p =	0.42					
Drug = Multiple							
Shen et al, ³⁴ 2021	12	27		0.444	[0.255; 0.647]	15.8%	15.3%
Common effect model		171	-	0.199	[0.139; 0.266]	100.0%	
Random effects model				0.216	[0.097; 0.362]		100.0%
Heterogeneity: $I^2 = 74\%$, $\tau^2 =$	= 0.0304, p	< 0.01	0.1 0.2 0.3 0.4 0.5 0.6 0.7				

Heterogeneity: $l^2 = 74\%$, $\tau^2 = 0.0304$, p < 0.01 0.1 0.2 0.3 0.4 0.5 0.6 0.7 Test for subgroup differences (fixed effect): $\chi_4^2 = 21.19$, df = 4(p < 0.01) Test for subgroup differences (random effects): $\chi_4^2 = 20.75$, df = 4(p < 0.01)

В

Study	Events	Total	Proportio	n 95%–Cl	Weight (common)	Weigh (random)
Drug = Sintilimab			:			
Zhang et al, 40 2021	20	30		[0.472; 0.827]	11.7%	10.3%
Duan et al, 27 2021	2	8 -	0.2		3.3%	5.9%
Common effect model		38	0.5		14.9%	
Random effects model			0.43	2 [0.121; 0.868]		16.1%
Heterogeneity: $I^2 = 76\%, \tau^2$	= 0.0598, p	= 0.04		n / a		
Drug = Pembrolizumab						
Huang et al, 29 2021	12	23	0.52	[0.306; 0.732]	9.0%	9.4%
Drug = Multiple						
Wu et al, 37 2021	13	19	0.68	4 [0.434; 0.874]	7.5%	8.8%
Shen et al, 34 2021	12	27	0.44	4 [0.255; 0.647]	10.5%	9.9%
Common effect model		46	0.54	5 [0.396; 0.689]	18.0%	
Random effects model			0.5	7 [0.323; 0.779]		18.8%
Heterogeneity: $I^2 = 60\%$, τ^2	= 0.0161, p	= 0.12				
Drug = Toripalimab	-	10			7.40/	0.00
He et al, 42 2021	5	18	0.2	• • •	7.1%	8.6%
Zhang et al, ²⁵ 2020	19	24	0.79	• • •	9.4%	9.6%
Common effect model		42	0.5	a , a	16.4%	
Random effects model Heterogeneity: $I^2 = 91\%$, τ^2	= 0.1209, p	< 0.01	0.54	5 [0.083; 0.964]		18.2%
Drug = Camrelizumab						
Ma et al, 32 2021	7	21		3 [0.146; 0.570]	8.2%	9.1%
Yang et al, 47 2021	18	23	0.7	3 [0.563; 0.925]	9.0%	9.4%
Liu et al, 43 2021	27	51	0.5	9 [0.385; 0.671]	19.7%	11.6%
Yang et al, 39 2021	7	12	0.58	3 [0.277; 0.848]	4.8%	7.2%
		107	0.5	5 [0.457; 0.651]	41.7%	
Common effect model			0.5	9 [0.371; 0.739]		37.5%
Random effects model	= 0.0231, p	= 0.03				
Common effect model Random effects model Heterogeneity: $J^2 = 68\%$, τ^2 Common effect model	= 0.0231, p	= 0.03 256	0.5	8 [0.495; 0.621]	100.0%	

Test for subgroup differences (fixed effect): $\chi_4^2 = 0.30$, df = 4 (p = 0.99) Test for subgroup differences (random effects): $\chi_4^2 = 0.14$, df = 4 (p = 1.00)

C					Weight	Weigh
Study	Events	Total	Proportion	95%-CI	(common)	(random
Drug = Sintilimab						
Zhang et al, 40 2021	9	30	0.300	[0.147; 0.494]	11.7%	9.9%
Duan et al, 27 2021	2	8	0.250	[0.032; 0.651]	3.3%	6.6%
Common effect model		38	0.284	[0.143; 0.447]	14.9%	-
Random effects model			0.284	[0.143; 0.447]		16.5%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$), <i>p</i> = 0.86					
Drug = Pembrolizumab						
Huang et al, 29 2021	2	23	0.087	[0.011; 0.280]	9.0%	9.4%
Drug = Multiple						
Wu et al, 37 2021	6	19	0.316	[0.126; 0.566]	7.5%	8.99
Shen et al, 34 2021	3	27	0.111	[0.024; 0.292]	10.5%	9.79
Common effect model		46	0.186	[0.082; 0.316]	18.0%	-
Random effects model			0.197	[0.037; 0.428]		18.79
Heterogeneity: $I^2 = 64\%$, $\tau^2 =$	0.0193, <i>p</i>	= 0.10				
Drug = Toripalimab						
He et al, 42 2021	7	18	0.389		7.1%	8.89
Zhang et al, ²⁵ 2020	5	24	0.208	L	9.4%	9.5%
Common effect model		42	0.281	a / a	16.4%	-
Random effects model Heterogeneity: $I^2 = 35\%$, $\tau^2 =$	0.0065, p	= 0.21	0.286	[0.127; 0.475]		18.39
Drug = Camrelizumab						
Ma et al, ³² 2021	13	21	0.619	[0.384; 0.819]	8.2%	9.2%
Yang et al, 47 2021	0	23	0.000	[0.000; 0.148]	9.0%	9.4%
Liu et al, 43 2021	17	51	0.333	[0.208; 0.479]	19.7%	10.89
Yang et al, 39 2021	3	12	0.250	[0.055; 0.572]	4.8%	7.79
Common effect model		107	0.267	[0.184; 0.358]	41.7%	-
Random effects model			0.255	[0.027; 0.585]		37.1%
Heterogeneity: $I^2 = 90\%$, $\tau^2 =$	0.0988, <i>p</i>	< 0.01				
Common effect model		256	0.237	[0.184; 0.294]	100.0%	-

Test for subgroup differences (random effects): $\chi_4^2 = 4.47$, df = 4(p = 0.35)

D

Study	Events	Total		Proportion	95%-CI	Weight (common)	Weight (random)
Drug = Sintilimab			<u>.</u>				
Zhang et al, 40 2021	20	30		0.667	[0.472; 0.827]	10.6%	9.6%
Duan et al, 27 2021	20	8		0.625	[0.245; 0.915]	2.9%	9.0 % 4.7%
Common effect model	5	38		0.662	[0.496; 0.812]	13.5%	4.1 /
Random effects model		50		0.662	[0.496; 0.812]	13.370	14.3%
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0, <i>p</i> = 0.79			0.002	[0.430, 0.012]		14.07
Drug = Toripalimab							
Xing et al, 28 2021	18	27		0.667	[0.460; 0.835]	9.5%	9.2%
He et al, 42 2021	11	18		0.611	[0.357; 0.827]	6.4%	7.6%
Zhang et al, 23 2020	19	24		0.792	[0.578; 0.929]	8.5%	8.8%
Common effect model		69		0.699	[0.582; 0.805]	24.4%	
Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0.0 = 0.42			0.699	[0.582; 0.805]		25.6%
neterogeneity. 7 = 0 %, t =	0, μ = 0.42						
Drug = Pembrolizumab			i				
Huang et al, ²⁹ 2021	20	23		0.870	[0.664; 0.972]	8.1%	8.6%
Drug = Multiple			i i i				
Wu et al, 37 2021	13	19		0.684	[0.434; 0.874]	6.7%	7.8%
Shen et al, 34 2021	24	27		0.889	[0.708; 0.976]	9.5%	9.2%
Common effect model		46		0.814	[0.684; 0.918]	16.3%	
Random effects model				0.803	[0.572; 0.963]		17.1%
Heterogeneity: $I^2 = 64\%$, τ^2	= 0.0193, <i>p</i> =	= 0.10	i				
Drug = Camrelizumab			, I				
Ma et al, 32 2021	8	21 —	i	0.381	[0.181; 0.616]	7.4%	8.2%
Yang et al, 47 2021	19	23		0.826	[0.612; 0.950]	8.1%	8.6%
Liu et al, 43 2021	34	51		0.667	[0.521; 0.792]	17.8%	11.6%
Yang et al, 39 2021	7	12		0.583	[0.277; 0.848]	4.3%	6.1%
Common effect model		107		0.643	[0.546; 0.734]	37.7%	
Random effects model				0.628	[0.435; 0.802]		34.5%
Heterogeneity: $I^2 = 69\%, \tau^2$	= 0.0246, <i>p</i> =	= 0.02					
Common effect model		283	+	0.709	[0.652; 0.763]	100.0%	
Random effects model				0.705	[0.620; 0.785]		100.0%

Test for subgroup differences (fixed effect) $\chi_4^2 = 8.40$, df = 4(ρ = 0.08) Test for subgroup differences (random effects): $\chi_4^2 = 5.27$, df = 4(ρ = 0.26)

Ε

Study	Events	Total		Proportion	95%-CI	Weight (common)	Weight (random)
Drug = Sintilimab							
Zhang et al, 40 2021	29	30		0.967	[0.828; 0.999]	12.8%	12.2%
Drug = Pembrolizumab							
Duan et al, 27 2021	7	8		0.875	[0.473; 0.997]	3.6%	4.8%
Drug = Multiple			i				
Wu et al, 37 2021	19	19		1.000	[0.824; 1.000]	8.2%	9.1%
Shen et al, 34 2021	27	27		1.000	[0.872; 1.000]	11.6%	11.5%
Common effect model		46		1.000	[0.959; 1.000]	19.7%	
Random effects model				1.000	[0.959; 1.000]		20.6%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$), <i>p</i> = 0.90						
Drug = Toripalimab							
He et al, 42 2021	18	18		1.000	[0.815; 1.000]	7.8%	8.8%
Zhang et al, 25 2020	24	24		1.000	[0.858; 1.000]	10.3%	10.7%
Common effect model		42		1.000	[0.955; 1.000]	18.1%	
Random effects model				1.000	[0.955; 1.000]		19.4%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$), <i>p</i> = 0.92						
Drug = Camrelizumab							
Ma et al, 32 2021	21	21	_	1.000	[0.839; 1.000]	9.0%	9.8%
Yang et al,47 2021	19	23		0.826	[0.612; 0.950]	9.9%	10.4%
Liu et al, 43 2021	51	51		1.000	[0.930; 1.000]	21.6%	16.3%
Yang et al, 39 2021	12	12		1.000	[0.735; 1.000]	5.3%	6.5%
Common effect model		107		0.990	[0.953; 1.000]	45.8%	
Random effects model				0.984	[0.890; 1.000]		42.9%
Heterogeneity: $I^2 = 69\%$, $\tau^2 =$	0.0217, p =	= 0.02					
Common effect model		233		0.994	[0.972; 1.000]	100.0%	
				0.992	[0.962; 1.000]		100.0%

eFigure 5. Forest plot of the outcomes for safety in neoadjuvant immunotherapy combined with chemotherapy in ESCC stratified by ICI types. (A) the incidence of tr-SAE, (B) R0 surgical resection rate. CI, confidence interval; ESCC, esophageal squamous cell carcinoma; ICI, immune-checkpoint inhibitors; tr-SAE, treatment-related severe adverse events

Α								В						Mainha	M-1-64
	_					Weight	Weight	Study	Events	Total		Proportion	95%-CI	Weight (common)	Weight (random)
Study	Events	Total		Proportion	95%-CI	(common)	(random)	Drug = Sintilimab			:				
			1					Zhang et al, 40 2021	23	23	!!	1.000	[0.852; 1.000]	4.8%	5.3%
Drug = Sintilimab								Duan et al, 27 2021	16	17	<u>_</u>	0.941	[0.713; 0.999]	3.6%	4.4%
Zhang et al, 41 2021	1	30	I	0.033	[0.001; 0.172]	7.6%	8.4%	Gu et al, 23 2020	15	15		1.000	[0.782; 1.000]	3.2%	4.0%
Duan et al, 27 2021	7	23		0.304	[0.132; 0.529]	5.8%	7.9%	Zhang et al, 41 2021	39	40		0.975	[0.868; 0.999]	8.2%	7.3%
Gu et al, 23 2020	6	17		0.353	[0.142; 0.617]	4.3%	7.3%	Common effect model		95		0.988	[0.945; 1.000]	19.7%	
Common effect model	0	70		0.172		17.7%		Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0 0 - 0 66			0.988	[0.945; 1.000]		21.0%
		70	1		[0.088; 0.274]			Hereiogeneity: 7 = 076, t =	0, p = 0.00		1				
Random effects model				0.199	[0.025; 0.459]		23.6%	Drug = Toripalimab			i				
Heterogeneity: $I^2 = 82\%$, τ^2	= 0.0453, <i>p</i>	< 0.01						Xing et al, 28 2021	11	11		1.000	[0.715; 1.000]	2.3%	3.2%
			I					He et al, 42 2021	14	16	· · · · · · · · · · · · · · · · · · ·	0.875	[0.617; 0.984]	3.4%	4.2%
Drug = Pembrolizumab			i i					Liu et al, 31 2021	18	18		1.000	[0.815; 1.000]	3.8%	4.6%
Huang et al, 29 2021	9	23	· · · · · · · · · · · · · · · · · · ·	0.391	[0.197; 0.615]	5.8%	7.9%	Common effect model Random effects model		45		0.978	[0.897; 1.000]	9.5%	40.0%
	0	20		0.001	[0.107, 0.010]	0.070	1.070	Heterogeneity: $I^2 = 33\%$, $\tau^2 =$	- 0.0090 p -	0.22		0.978	[0.871; 1.000]		12.0%
			I. I					Hereiogeneity: 7 = 55%, t	= 0.000 <i>0</i> , <i>p</i> =	0.22	i				
Drug = Toripalimab								Drug = Pembrolizumab			i				
He et al, 42 2021	4	20		0.200	[0.057; 0.437]	5.1%	7.6%	Huang et al, 29 2021	21	21		1.000	[0.839; 1.000]	4.4%	5.0%
								Shang et al, 33 2021	29	29		1.000	[0.881; 1.000]	6.0%	6.1%
Drug = Camrelizumab			I. I					Common effect model		50		1.000	[0.962; 1.000]	10.4%	
Ma et al, 32 2021	1	21		0.048	[0.001; 0.238]	5.3%	7.7%	Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0			1.000	[0.962; 1.000]		11.2%
Liu et al, 44 2022	34	60		0.567	[0.432; 0.694]	15.0%	9.3%	Heterogeneity. 7 = 0 %, 1 =	0, p = 0.91						
								Drug = Multiple							
Xu et al, 46 2022	7	46		0.152	[0.063; 0.289]	11.5%	9.0%	Wu et al, 37 2021	35	38		0.921	[0.786; 0.983]	7.8%	7.1%
Wang et al, 36 2021	11	30		0.367	[0.199; 0.561]	7.6%	8.4%	Shen et al, 34 2021	26	27	<u></u> _	0.963	[0.810; 0.999]	5.6%	5.9%
Liu et al, 43 2021	6	56		0.107	[0.040; 0.219]	14.0%	9.2%	Common effect model		65		0.940	[0.864; 0.989]	13.4%	
Common effect model		213		0.255	[0.197; 0.317]	53.5%		Random effects model				0.940	[0.864; 0.989]		13.0%
Random effects model				0.230	[0.073; 0.436]		43.6%	Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0, p = 0.56						
Heterogeneity: $I^2 = 91\%$, τ^2	0.0522 p	- 0.01		01200	[01010, 01100]		101070	Drug = Tislelizumab							
Heterogeneity. 7 = 91%, t	= 0.0555, p	< 0.01						Yan et al, 38 2021	35	36		0.972	[0.855; 0.999]	7.4%	6.9%
			I												
Drug = Tislelizumab								Drug = Camrelizumab							
Yan et al, 38 2021	15	43	÷	0.349	[0.210; 0.509]	10.8%	8.9%	Wang et al, 35 2021	12	12	e	1.000	[0.735; 1.000]	2.5%	3.4%
			I					Liu et al, 44 2022	50	51 46	 _	0.980	[0.896; 1.000]	10.5%	8.2%
Drug = Multiple			i i					Xu et al, ⁴⁶ 2022 Yang et al, ⁴⁷ 2021	37 20	46 20		0.804	[0.661; 0.906] [0.832; 1.000]	9.5% 4.2%	7.8% 4.9%
Shen et al, 34 2021	2	20		0.071	[0 000: 0 225]	7.1%	0.20/	Liu et al, ⁴³ 2021	51	51		1.000	[0.930; 1.000]	4.2 %	8.2%
Sherrer al, ³⁴ 2021	2	28		0.071	[0.009; 0.235]	7.1%	8.3%	Yang et al, 30 2021	12	12		1.000	[0.735; 1.000]	2.5%	3.4%
			I					Common effect model		192	-	0.977	[0.945; 0.997]	39.6%	
Common effect model		397	-	0.238	[0.196; 0.283]	100.0%		Random effects model				0.982	[0.915; 1.000]		35.9%
Random effects model				0.227	[0.133; 0.335]		100.0%	Heterogeneity: $I^2 = 72\%$, $\tau^2 =$	= 0.0180, <i>p</i> <	0.01					
					-						1			100.00	
Heterogeneity: $I^2 = 84\%$, τ^2	= 0.0334, <i>p</i>	< 0.01	0.1 0.2 0.3 0.4 0.5 0.6					Common effect model Random effects model		483	1	0.980 0.981	[0.961; 0.994] [0.956; 0.997]	100.0%	100.0%
Test for subgroup difference	s (fixed effe	ct): $\chi_5^2 = 12$.	36, df = $5(p = 0.03)$									0.981	[0.936; 0.997]		100.0%
Test for subgroup difference	s (random e	effects): χ_5^2 =	10.64, df = 5(p = 0.06)					Heterogeneity: $I^2 = 36\%$, $\tau^2 =$ Test for subgroup differences			0.65 0.7 0.75 0.8 0.85 0.9 0.95 1 df = 5(p = 0.58)				

Test for subgroup differences (random effects): $\chi_c^2 = 3.72$, df = 5(p = 0.59)

eFigure 6. Sensitivity analyses of the outcomes by repeating the pooled analyses with one study omitted at a time. (A) pCR rate, (B) MPR rate, (C) the incidence of tr-SAE, (D) R0 surgical resection rate. CI, confidence interval; pCR, pathological complete response; MPR, major pathological response; tr-SAE, treatment-related severe adverse events

Α					В							
Study			Proportion	95%-CI	_							
Omitting Ma et al, ³² 2021		-	- 0.31	[0.27; 0.35]	Study						Proportion	95%-CI
Omitting Yan et al, ³⁸ 2021			0.30	[0.26; 0.34]								
Omitting Lee et al, ²¹ 2019			0.31	[0.27; 0.35]	Omitting Shang et al, 33 2021						0.47	[0.40; 0.54]
Omitting Shang et al, ³³ 2021			0.31	[0.27; 0.35]	Omitting Yan et al, 38 2021						0.47	[0.40; 0.53]
Omitting Liu et al, 44 2022			0.31	[0.27; 0.35]	Omitting Wang et al, 36 2021					_	0.48	[0.41; 0.56]
Omitting Xing et al, 28 2021			0.31	[0.27; 0.35]	Omitting Gu et al, 23 2020					_	0.49	[0.42; 0.56]
Omitting Duan et al, 27 2021		+++++++++++++++++++++++++++++++++++++++	- 0.31	[0.27; 0.35]	0							. , .
Omitting Liu et al, 43 2021			- 0.31	[0.27; 0.35]	Omitting Duan et al, 27 2021						0.49	
Omitting Wu et al, 37 2021			- 0.31	[0.27; 0.35]	Omitting Zhang et al, 40 2021						0.49	[0.41; 0.56]
Omitting Liu et al, ²³ 2021			- 0.31	[0.27; 0.35]	Omitting Yang et al, 47 2021						0.49	[0.42; 0.56]
Omitting Shen et al, ³⁴ 2021			- 0.31	[0.27; 0.35]	Omitting Zhang et al, 25 2020						0.49	[0.42; 0.56]
Omitting Yang et al, 39 2021			- 0.31	[0.27; 0.35]	Omitting Xu et al, 46 2022						0.49	[0.42; 0.56]
Omitting van den Ende et al, 22 2019			- 0.31	[0.27; 0.36]	Omitting Zhang et al, 41 2021						0.49	[0.42; 0.56]
Omitting Wang et al, ³⁶ 2021			- 0.31	[0.27; 0.36]								
Omitting Gu et al, ²³ 2020			- 0.31	[0.27; 0.36]	Omitting He et al, 42 2021						0.49	[0.42; 0.56]
Omitting Wang et al, ³⁵ 2021 Omitting Zhang et al, ⁴¹ 2021			- 0.31 - 0.32	[0.28; 0.36] [0.28; 0.36]	Omitting Li et al, 30 2021						0.49	L
Omitting Yang et al, ⁴⁷ 2021			- 0.32	[0.28; 0.36]	Omitting Wu et al, 37 2021						0.49	[0.42; 0.57]
Omitting Li et al, ³⁰ 2021			- 0.32	[0.28; 0.36]	Craitting Wang et al, 35 2021						0.49	[0.42; 0.56]
Omitting Zhang et al, ²⁵ 2021			- 0.32	[0.28; 0.36]	Omitting Yang et al, 39 2021						0.49	• • •
Omitting Xu et al, ⁴⁶ 2022			- 0.32	[0.28; 0.36]	Shifting Shen et al, 34 2021							on [0.425%56]
Semitting Sun et al, 45 2022		*****	- Proportion-	[0.295%-36]	-					+++++++++++++++++++++++++++++++++++++++		
Omitting He et al, 42 2021			- 0.32	[0.28; 0.36]	Omitting Liu et al, 43 2021 Omitting Zhang et al, 2021							99 [0.46:0.57] 99 [0.97;57]
Omitting Zhang et al, 40 2020			0.32	[0.28; 0.36]	Omitting Duan et al, 27 2021							99 [0.97; 1]
Omitting Liu et al, 44 2022			0.24	[0.15; 0.35]	Ranidion effects model ¹					_		99[0.42;90.56]
Chaittingni hitergt stran, del 2021			- 092361	[0.23; 0.38]	Omitting Huang et al, ²⁹ 2021	I		I		1		99 [0.97; 1]
Omitting Wang et al, ³⁶ 2021	-0.3 -0.2 -0.1	0 0.1 0.2 0.3	0.26	[0.15; 0.38]	Omitting Wu et al, ³⁷ 2021 Omitting He et al, ⁴² 2021	-0.4	-0.2	0	0.2	0.4		99 [0.97; 1] 99 [0.97; 1]
Omitting Gu et al, ²³ 2020	0.0 0.2 0.1		0.26	[0.16; 0.38]	Omitting Gu et al, ²³ 2020							99 [0.97; 1]
Omitting Yan et al, ³⁸ 2021			0.26	[0.15; 0.38]	Omitting Yan et al, 38 2021							99 [0.97; 1]
					Omitting Wang et al, 35 2021							99 [0.97; 1]
Omitting Duan et al, ²⁷ 2021			0.27	[0.16; 0.39]	Omitting Liu et al, 44 2022							99 [0.97; 1]
Omitting He et al, ⁴² 2021			0.27	[0.17; 0.40]	Omitting Zhang et al, ⁴¹ 2021							99 [0.97; 1]
Omitting Xu et al, ⁴⁶ 2022			0.28	[0.17; 0.40]	Omitting Xu et al, ⁴⁶ 2022 Omitting Liu et al, ³¹ 2021						_	99 [0.98; 1] 99 [0.97; 1]
Omitting Liu et al, 56 2021			0.28	[0.18; 0.41]	Omitting Yang et al, ⁴⁷ 2021							99 [0.97; 1]
Omitting Shen et al, ³⁴ 2021			0.29	[0.18; 0.40]	Omitting Shang et al, ³³ 2021						-	99 [0.96; 1]
Omitting Ma et al, ³² 2021					Omitting Liu et al, 56 2021							98 [0.96; 1]
5			0.29	[0.18; 0.40]	Omitting Shen et al, ³⁴ 2021							99 [0.97; 1]
Omitting Zhang et al, 40 2021			0.29	[0.19; 0.41]	Omitting Yang et al, 39 2021							99 [0.97; 1]
Omitting Athauda et al, ²⁶ 2021			0.25	[0.15; 0.36]	Omitting Sun et al, 45 2022							99 [0.96; 1]
Omitting Sun et al, ⁴⁵ 2022			0.25	[0.15; 0.36]	Omitting Li et al, ³⁰ 2021 Omitting van den Ende et al, ²² 2019							99 [0.96; 1] 99 [0.96; 1]
•					Omitting Athauda et al, ²⁶ 2021							.99 [0.98, 1] .99 [0.97; 1]
Random effects model			0.27	[0.17; 0.38]								[0.57, 1]
	· · · · ·		0.27	[0.17, 0.30]	Random effects model		_				• 0.	99 [0.97; 1]
_	0.4 -0.2	0 0.2 0.	4				-0.5		0	0.5		
	0.7 0.2	0.2 0.2	т				-0.5		U	0.5		

eFigure 7. Sensitivity analyses based on the stage of disease in ESCC. (A) pCR rate, (B) MPR rate, (C) R0 surgical resection rate. (D) ORR, (E) DCR. CI, confidence interval; ESCC, esophageal squamous cell carcinoma; pCR, pathological complete response; MPR, major pathological response; ORR, objective response rate; DCR, disease control rate

Α

5 Stage = Relative ly advanced Zhang et al, ²⁵ 2020		Total		Proportion	95%-CI	Weight (common)	Weight							
Zhang et al, 25 2020						(continion)	(random)	Study	Events	Total		Proportion	95%-CI	Weight (common)
	2							Stage = Relatively advan	and					
	3	18		0.167	[0.036; 0.414]	9.9%	10.7%		cea	10				
Zhang et al, 40 2021	10	40		0.250	[0.127; 0.412]	21.8%	21.4%	Zhang et al, 25 2020	9	18		0.500	[0.260; 0.740]	15.7%
Nu et al, 37 2021	13	38		0.342	[0.196; 0.514]	20.7%	20.5%	Zhang et al, 40 2021	12			0.522	[0.306; 0.732]	20.0%
He et al,42 2021	3	16		0.188	[0.040; 0.456]	8.9%	9.6%	Wu et al, 37 2021	16	38		0.421	[0.263; 0.592]	32.8%
rang et al, 39 2021	5	20		0.250	[0.087; 0.491]	11.0%	11.7%	He et al,42 2021	7	16		0.438	[0.198; 0.701]	14.0%
iu et al, 4 2022	20	51		0.392	[0.258; 0.539]	27.7%	26.1%	Yang et al, 39 2021	10	20		0.500	[0.272; 0.728]	17.4%
Common effect model	20	183		0.291	[0.225; 0.361]	100.0%		Common effect model		115		0.469	[0.376; 0.564]	100.0%
Random effects model		100			[0.217; 0.364]		100.0%	Random effects model				0.469	[0.376; 0.564]	
deterogeneity: $I^2 = 2\%$, $\tau^2 = 0.00$	011, p = 0	.40	i	0.200	[0.217, 0.304]		100.070	Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$), <i>p</i> = 0.94		l i			
Common effect model		183	i	0.291	[0.225; 0.361]	100.0%		Common effect model		115		0.469	[0.376; 0.564]	100.0%
Random effects model		100			[0.217; 0.364]		100.0%	Random effects model				0.469	[0.376; 0.564]	
Heterogeneity: $I^2 = 2\%$, $\tau^2 = 0.00$ Test for subgroup differences (fixe			0.1 0.2 0.3 0.4 0.5	0.200	[0.217, 0.304]		100.078	Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$ Test for subgroup differences	(fixed effect	0.2 0.3 t): $\chi_0^2 = 0.00$, df = 0(p = NA) ffects): $\chi_0^2 = 0.00$, df = 0(p = NA)	0.4 0.5 0.6 0.7			

Weight 95%-CI (common)

16.5%

27.0%

11.6%

8.8%

36.1%

100.0%

100.0%

Test for subgroup differences (random effects): $\chi_0^2 = 0.00$, df = 0(p = NA)

С

Study	Events	Total	Proportion	
Stage = Relative ly advan	ced		1	
Zhang et al, 40 2021	23	23		[0
Wu et al, 37 2021	35	38	0.921	[0.
He et al,42 2021	14	16	0.875	[0.
Yang et al, 39 2021	12	12	1.000	[0.
Liu et al, 44 2022	50	51	0.980	[0.
Common effect model		140	0.972	[0.9
Random effects model			0.972	[0.9
Heterogeneity: $I^2 = 23\%$, $\tau^2 =$	0.0024, p =	= 0.27		
Common effect model		140	0.972	[0.9
Random effects model			0.972	[0.9

Heterogeneity: $l^2 = 23\%$, $\tau^2 = 0.0024$, p = 0.270.65 0.7 0.75 0.8 0.85 0.9 0.95 1 Test for subgroup differences (fixed effect): $\chi_0^2 = 0.00$, df = 0(p = NA) Test for subgroup differences (random effects): $\chi_0^2 = 0.00$, df = 0(p = NA)

D

Weight (random)	Study	Events	Total		95%-CI	Weight (common)	Weight (random)				
17.9% 26.2% 13.3% 10.4% 32.2%	Stage = Relative ly a dvan Zhang et al, ⁴⁰ 2021 Wu et al, ³⁷ 2021 He et al, ⁴² 2021 Yang et al, ³⁸ 2021 Common effect model Random effects model Heterogeneity: $J^2 = 0\%, \tau^2 =$	20 13 11 7	30 19 18 12 79					0.667 0.684 0.611 0.583 0.647 0.647	[0.472; 0.827] [0.434; 0.874] [0.357; 0.827] [0.277; 0.848] [0.534; 0.753] [0.534; 0.753]	37.7% 24.1% 22.8% 15.4% 100.0%	37.7% 24.1% 22.8% 15.4% 100.0%
100.0%	Common effect model Random effects model Heterogeneity: $I^2 = 0\%, \tau^2 =$ Test for subgroup differences Test for subgroup differences	(fixed effec			5 0.6	0.7	0.8	0.647 0.647	[0.534; 0.753] [0.534; 0.753]	100.0% 	 100.0%

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Weight (random)

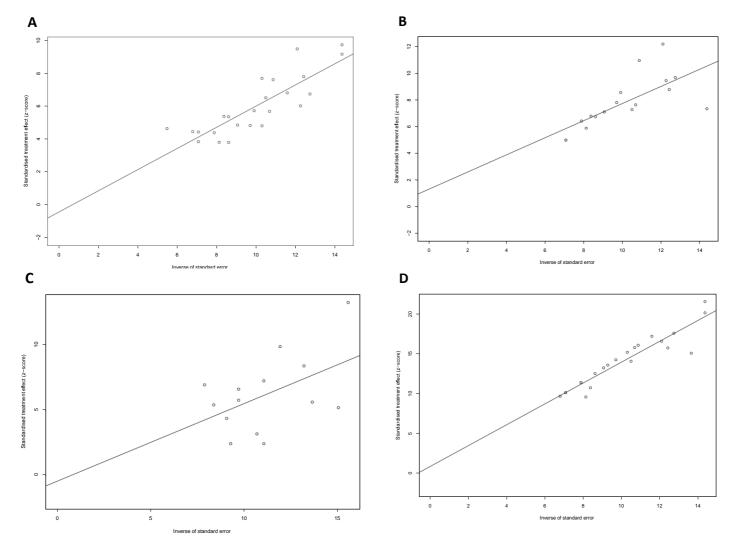
> 15.7% 20.0% 32.8% 14.0% 17.4% 100.0%

---100.0%

E					
Study	Events	Total	Proportion 95%	Weight CI (common)	Weight (random)
Stage = Relative ly adva	nced				
Zhang et al,25 2020	24	24	1.000 [0.858; 1.0	23.2%	23.2%
Zhang et al,40 2021	29	30	0.967 [0.828; 0.9	999] 28.9%	28.9%
Wu et al,37 2021	19	19	1.000 [0.824; 1.0	000] 18.5%	18.5%
He et al,42 2021	18	18	1.000 [0.815; 1.0	000] 17.5%	17.5%
Yang et al,39 2021	12	12	1.000 [0.735; 1.0	000] 11.8%	11.8%
Common effect model		103	0.997 [0.964; 1.0	100.0%	
Random effects model			0.997 [0.964; 1.0	[000	100.0%
Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0, <i>p</i> = 0.91				
Common effect model		103	0.997 [0.964; 1.0	000] 100.0%	
Random effects model			0.997 [0.964; 1.0	[000	100.0%

 $\begin{array}{l} \mbox{Heterogeneity:} \ l^2=0\%, \ r^2=0, \ p=0.91 & 0.75 & 0.8 \\ \mbox{Test for subgroup differences (fixed effect):} \ \chi^2_0=0.00, \ df=0 \ (p=NA) \\ \mbox{Test for subgroup differences (random effects):} \ \chi^2_0=0.00, \ df=0 \ (p=NA) \end{array}$ 0.75 0.8 0.85 0.9 0.95 1

eFigure 8. Egger's tests of the outcomes to detect publication bias. (A) pCR rate, (B) MPR rate, (C) the incidence of tr-SAE, (D) R0 surgical resection rate. CI, confidence interval; pCR, pathological complete response; MPR, major pathological response; tr-SAE, treatment-related severe adverse events



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eFigure 9. Forest Plot of Safety Outcomes of Neoadjuvant Immunotherapy Combined With Chemotherapy

Α								В				R0 surgica		Weight	Weight
				The incidence		Weight	Weight	Study	Events	Total		resection Ra			(random)
Study	Events	Total		of tr-SAE	95%-CI	(common)	(random)	Histology = ESCC			i				
Histology = ESCC								Zhang et al,40 2021	23	23		1.000	[0.852; 1.000]	3.9%	4.3%
	24	~~~		0.507	0 400 0 0041	10.00/	7.00/	Duan et al,27 2021	16	17		0.941	[0.713; 0.999]	2.9%	3.5%
Liu et al,44 2022	34	60			[0.432; 0.694]	13.3%	7.9%	Xing et al, ²⁸ 2021	11	11		1.000	[0.715; 1.000]	1.9%	2.5%
Huang et al,29 2021	9	23			[0.197; 0.615]	5.2%	6.9%	Huang et al, 29 2021	21	21 38		1.000	[0.839; 1.000]	3.6%	4.1% 5.9%
Wang et al, ³⁶ 2021	11	30			[0.199; 0.561]	6.7%	7.2%	Wu et al, ³⁷ 2021 He et al, ⁴² 2021	35 14	30		0.921 0.875	[0.786; 0.983] [0.617; 0.984]	6.5% 2.8%	3.4%
Gu et al, ²³ 2020	6	17	· · ·	0.353	[0.142; 0.617]	3.9%	6.4%	Gu et al. ²³ 2020	14	16 —		1.000	[0.782; 1.000]	2.6%	3.4%
Yan et al,38 2021	15	43		0.349	[0.210; 0.509]	9.6%	7.6%	Yan et al. ³⁸ 2021	35	36		0.972	[0.855; 0.999]	6.1%	5.7%
Duan et al,27 2021	7	23		0.304	[0.132; 0.529]	5.2%	6.9%	Wang et al. ³⁶ 2021	12	12		1.000	[0.735; 1.000]	2.1%	2.7%
He et al,42 2021	4	20		0.200	[0.057; 0.437]	4.5%	6.7%	Liu et al,44 2022	50	51		0.980	[0.896; 1.000]	8.6%	6.8%
Xu et al,46 2022	7	46	<u>_</u>	0.152	[0.063; 0.289]	10.2%	7.7%	Zhang et al,41 2021	39	40		0.975	[0.868; 0.999]	6.8%	6.0%
Liu et al.56 2021	6	56			[0.040; 0.219]	12.4%	7.8%	Xu et al, ¹⁶ 2022	37	46	!	0.804	[0.661; 0.906]	7.8%	6.5%
Shen et al.34 2021	2	28			[0.009; 0.235]	6.3%	7.2%	Liu et al, ³¹ 2021	18	18		1.000	[0.815; 1.000]	3.1%	3.7%
Ma et al.32 2021	1	21			[0.001; 0.238]	4.7%	6.8%	Yang et al,47 2021	20	20		1.000	[0.832; 1.000]	3.4%	3.9%
Zhang et al,40 2021	1	30			[0.001; 0.233]	6.7%	7.2%	Shang et al,33 2021	29	29	i®	1.000	[0.881; 1.000]	4.9%	5.0%
• ·	'	397						Liu et al,56 2021	51	51	iU	1.000	[0.930; 1.000]	8.6%	6.8%
Common effect model		397			[0.196; 0.283]	88.8%		Shen et al, ³⁴ 2021 Yang et al, ³⁸ 2021	26 12	27 12		0.963	[0.810; 0.999]	4.6% 2.1%	4.8% 2.7%
Random effects model				0.227	[0.133; 0.335]		86.4%	Common effect model	12	483	i	1.000 0.980	[0.735; 1.000] [0.961; 0.994]	2.1% 82.6%	2.7%
Heterogeneity: I^2 = 84%, t^2	= 0.0334, p	< 0.01	i					Random effects model		403			[0.956; 0.997]	02.070	81.8%
								Heterogeneity: $I^2 = 36\%$, $t^2 = 0.01$	061 n = 0.0	R	, i	0.301	[0.330, 0.331]		01.078
Histology = EAC								notorogonotyri contra con	00 () p 010	~					
Athauda et al,26 2021	9	15		0.600	[0.323; 0.837]	3.4%	6.2%	Histology = EAC							
Sun et al.45 2022	19	35		0.543	[0.366; 0.712]	7.8%	7.4%	Sun et al,45 2022	26	26		1.000	[0.868; 1.000]	4.4%	4.7%
Common effect model		50			[0.417; 0.699]	11.2%		Li et al,30 2021	28	28		1.000	[0.877; 1.000]	4.8%	4.9%
Random effects model					[0.417; 0.699]		13.6%	van den Ende et al,22 2019	33	33		1.000	[0.894; 1.000]	5.6%	5.4%
Heterogeneity: $l^2 = 0\%$, $t^2 = 0\%$	0 0 - 0 73			01000	[01111] 01000]		101070	Athauda et al,28 2021	15	15		1.000	[0.782; 1.000]	2.6%	3.2%
Fieldiogeneity. 7 = 0 %, t =	0, p = 0.73							Common effect model		102		1.000	[0.980; 1.000]	17.4%	
								Random effects model				1.000	[0.980; 1.000]		18.2%
Common effect model		447	T		[0.229; 0.314]	100.0%		Heterogeneity: $l^2 = 0\%$, $t^2 = 0$, ρ	= 1.00		1				
Random effects model				0.269	[0.167; 0.383]		100.0%	Common effect model		585	1	0.986	[0.971; 0.996]	100.0%	
Heterogeneity: $l^2 = 85\%$, t^2	-0.0412 p	< 0.01	0.2 0.4 0.6 0.8					Random effects model		303	_		[0.967; 0.996]	100.0%	100.0%
Test for subgroup difference									062 0 = 0.0	D		0.001	[0.001, 0.009]		100.070
• 1								Test for subgroup differences (fixe	0.02, p = 0.0	= 3.52 df = 1 /n =	0.65 0.7 0.75 0.8 0.85 0.9 0.95 1				
Test for subgroup difference	s (random e	enects): X =	13.46, at = 1 ($p < 0.01$)					Test for subgroup differences (na	ndom effects	$\hat{v}_{r} = 2.88 \text{ df} = 1$	(n = 0.09)				
										/ /g =1.50; di = 1	· · · · · · · · · · · · · · · · · · ·				