晚期非小细胞肺癌患者 PD-1 使用的系统评价再评价

陈芝强[1],李泽云[1],黄睿澜[1],綦向军[1],陈国铭[1],刘惠平[2],孙玲玲[3,4],曹　洋[3,4],林丽珠[3,4]
(1. 广州中医药大学第一临床医学院，广东 广州 510405;2. 广州中医药大学针灸康复临床医学院，广东 广州 510006;3.广州中医药大学第一附属医院,广东 广州 510405;4.中国中医药循证医学中心肿瘤疾病项目组,北京 100000)

摘　要:[目的] 对目前公开发表的 PD-1/PD-L1 治疗晚期非小细胞肺癌的系统评价(systematic review,SR)/Meta 分析进行再评价,评估其报告质量、方法学质量及证据质量。[方法] 计算机检索 PubMed,EMBASE,the Cochrane Library,Clinical Trials,CNKI,VIP 和万方数据库,搜集 PD-1/PD-L1 治疗晚期非小细胞肺癌的 SR/Meta 分析,检索年限均为建库至 2020 年 7 月。采用 PRISMA 声明、AMSTAR 2 工具和 GRADE 方法分别评价所纳入 SR/Meta 分析的报告质量、方法学质量和证据质量。[结果] 最终纳入 25 个 SR/Meta 分析,包含 36 个结局指标。PRISMA 声明评价结果显示纳入研究多数存在一定的报告缺陷。AMSTAR 2 工具评价结果显示 25 个 SR/Meta 分析的质量等级均为极低，存在问题最多的 3 个关键条目是条目 2“是否有预先发表的方案,研究与方案是否有明显偏倚”、条目 4“是否使用全面的文献检索策略”、条目 7“是否提供排除文献的清单,并说明了排除理由”。GRADE 分级结果显示 SR/Meta 分析结局指标(包含亚组)的等级以低质量和中质量为主,导致降级的最主要因素为发表偏倚,其次为局限性以及不一致性。[结论] 当前证据显示 PD-1/PD-L1 或联合化疗治疗晚期非小细胞肺癌的循证医学证据多为低质量,相关 SR/Meta 分析的方法学质量及证据质量较差,规范性仍有待提高。

关键词:PD-1;PD-L1;非小细胞肺癌;系统评价;Meta 分析;再评价
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Re-evaluation of Systematic Reviews and Meta Analyses of PD-1/PD-L1 Related Therapy for Advanced Non-small Cell Lung Cancer

CHEN Zhi-qiang[1], LI Ze-yun[1], HUANG Rui-lan[1], QI Xiang-jun[1], CHEN Guo-ming[1], LIU Hui-ping[2], SUN Ling-ling[3,4], CAO Yang[3,4], LIN Li-zhu[3,4]
(1. The First Clinical Medical College of Guangzhou University of Chinese Medicine, Guangzhou 510405, China;2. Guangzhou University of Traditional Chinese Medicine Clinical College of Acupuncture and Rehabilitation, Guangzhou 510006, China;3. The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510405, China;4. Project Team of Cancer, Evidence-based Medicine Center of Chinese Medicine in China, Beijing 100000, China)

Abstract:[Purpose] To re-evaluate the quality of published systematic reviews and Meta analyses of PD-1/PD-L1 related therapy for advanced non-small cell lung cancer. [Methods] Systematic reviews and Meta analyses of PD-1/PD-L1 related therapy for advanced non-small cell lung cancer published before July 2020 were collected from PubMed, EMBASE, the Cochrane Library, Clinical Trials, CNKI, VIP and Wanfang databases. The quality of reporting items, methodologies and evidence of included systematic reviews and Meta analyses were assessed by PRISMA, AMSTAR 2 and GRADE, respectively. [Results] A total of 25 systematic reviews and Meta analyses included 36 outcomes were obtained. The evaluation of PRISMA showed that most of the included studies were insufficient on reporting items. The quality levels of included studies were very low according to AMSTAR 2. Most of the studies had deficiencies on Item 2 (Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol ?), Item 4 (Did the review authors use a comprehensive literature search strategy ?) and Item 7 (Did the review authors provide a list of excluded studies and justify the exclusions ?). Rated by the GRADE, the quality of outcomes (including outcomes of subgroups) was low or medium. The most important factors for downgrading were publication bias, followed by limitations and inconsistency. [Conclusion] This study suggests that the quality of published systematic reviews and Meta analyses of PD-1/PD-L1 related therapy or combined chemotherapy for advanced non-small cell lung cancer is unsatisfactory. The poor quality of methodology and evidence of included studies indicates that the standard of systematic reviews and Meta analyses of PD-1/PD-L1 related therapy for advanced non-small cell lung cancer should be improved.

Key words:PD-1;PD-L1;non-small cell lung cancer;systematic review;Meta analysis;re-evaluation

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通信作者:林丽珠,E-mail:13501505588@139.com

肺癌的发病率和死亡率在全球恶性肿瘤中均居首位[1]。非小细胞肺癌(non-small cell lung cancer,NSCLC)占肺癌的80%~85%,是全球恶性肿瘤死亡的重要原因[2]。目前晚期NSCLC的化疗及靶向治疗取得较大的进展,相应的靶向治疗可显著延长患者的生存时间[3],但化疗相关严重不良反应、获得性耐药仍然限制了化疗及靶向治疗的应用。因此,晚期NSCLC的治疗仍需探索更加有效、安全性高和耐药性低的治疗方式。近些年来免疫检查点的研究实现了突破性进展,针对阻断PD-1/PD-L1通路免疫检查点的治疗在晚期NSCLC中的临床前及临床研究中均获得显著的临床疗效,有效延长了患者的生存时间,提高了患者的生存率[4-5]。

近年来已完成了多个验证PD-1/PD-L1治疗晚期NSCLC总有效率(overall response rate,ORR)及相关不良反应的随机对照试验(randomized controlled trial,RCT),并已有多个基于PD-1/PD-L1治疗晚期NSCLC相关RCT的系统评价(systematic review,SR)和Meta分析发表,但相关证据不一。一项评估了2 037例NSCLC患者的Meta分析显示[6],PD-1/PD-L1抑制剂联合化疗一线治疗结果在ORR、总生存率(overall survival,OS)和无进展生存期(progression-free survival,PFS)上都显示出了显著的临床获益。而Zhou等[7]的一项Meta分析结果显示,PD-1/PD-L1抑制剂联合多西紫杉醇与单用多西紫杉醇相比,对PFS无明显影响(HR=0.83,95%CI:0.65~1.06,*P*=0.134)。相关SR、Meta分析在纳入人群、受试者例数、结局指标的选择等方面存在较大的差异,报告规范及方法学理解不够深入,导致PD-1/PD-L1治疗晚期NSCLC的循证医学证据质量不高,容易对临床决策者造成一定的误导。

本研究旨在采用科学的手段,对目前公开发表的PD-1/PD-L1治疗晚期NSCLC的SR、Meta分析进行再评价,评估其报告质量、方法学质量及证据质量,旨在倡导临床科研工作者重视并严格遵循SR/Meta分析的报告规范,提高报告质量,为PD-1/PD-L1治疗晚期NSCLC提供更可靠的循证医学证据。

1 资料与方法

1.1 纳入与排除标准

1.1.1 研究类型

所有与PD-1治疗晚期NSCLC相关的SR/Meta分析。

1.1.2 研究对象

经病理学和细胞学检查,明确诊断为Ⅲ~Ⅳ期的NSCLC患者,另外,不限研究对象的性别、年龄、种族、国籍、发病时间。

1.1.3 干预措施

试验组为PD-1治疗或PD-1联合常规治疗。对照组与PD-1无关,可为化疗等常规治疗、安慰剂或空白对照等。

1.1.4 结局指标

①评价疗效指标:ORR、OS和PFS;②评价不良反应指标:免疫介导的不良事件,有轻重不同,重者甚至导致死亡,其中≥3级的不良事件需要进行干预。纳入25篇文献着重对3级或以上不良反应和免疫相关不良事件如甲状腺功能减退、甲亢、皮疹、肺炎等进行评价。

1.1.5 排除标准

① 重复发表的文献(保留信息最全面或最新的一篇);②会议摘要;③无法获取全文者;④ 无法提取数据者;⑤ 非中、英文文献。

1.2 文献检索策略

计算机检索PubMed,EMBASE,the Cochrane Library,Clinical Trials,CNKI,VIP和万方数据库,检索年限均为建库至2020年7月。此外,追溯纳入文献的参考文献作为检索补充。根据不同数据库的特征,采取主题词和自由词相结合的方式进行检索。中文检索词包括:非小细胞肺癌、免疫治疗、PD-1抑制剂、PD-L1抑制剂、帕博利珠单抗、纳武单抗、阿特珠单抗、荟萃分析、Meta分析、系统评价、系统综述等;英文检索词包括:non-small cell lung cancer、NSCLC、PD-1、PD-L1、Pembrolizumab、Nivolumab、Atezolizumab、Meta analyses、Meta analysis、Meta-analysis、Systematic reviews、Systematic review等。使用Endnote软件8.2版管理文献资料。

1.3 文献筛选与资料提取

双人独立筛选文献、提取资料并交叉核对,如遇分歧,则由第三方协助判定,对于缺乏的资料,尽量与作者联系予以补充。资料提取内容主要包括:①纳入研究的基本信息,包括纳入文献类型(SR/Meta分析)、第一作者、发表年度、肿瘤类型、方法学质量评价、纳入的原始研究数量、患者例数等;②干预措施的具体细节;③所纳入研究中的所有指标及其结果

测量数据。

1.4 评价方法

1.4.1 报告质量评价

采用 PRISMA 声明[8](preferred reporting items for systematic reviews and Meta analyses,PRISMA)评价纳入的 SR/Meta 分析的报告质量。量表共有 27 个条目,每个条目根据作者是否报告作出判断,分为:完整报告、部分报告和未报告,并记录。

1.4.2 方法学质量评价

采用 AMSTAR[9]量表评价纳入的 SR/Meta 分析的方法学质量,结合关键条目得分,对总体质量进行分级。各条目评价包括“是”(正确且有充分依据)、“部分是”(正确但依据不充分)和“否”(无相关评价内容或评价不当)3 种答案。AMSTAR 2 量表含有 16 个条目,其中条目 2、4、7、9、11、13、15 为关键条目,方法学质量等级评价标准见表 1(Table 1)。

Table 1 Methodological quality assessment criteria

Quality rate	Weakness
High	Zero or one non-critical weakness
Moderate	More than one non-critical weakness
Low	One critical flaw with or without non-critical weaknesses
Critically low	More than one critical flaw with or without non-critical weaknesses

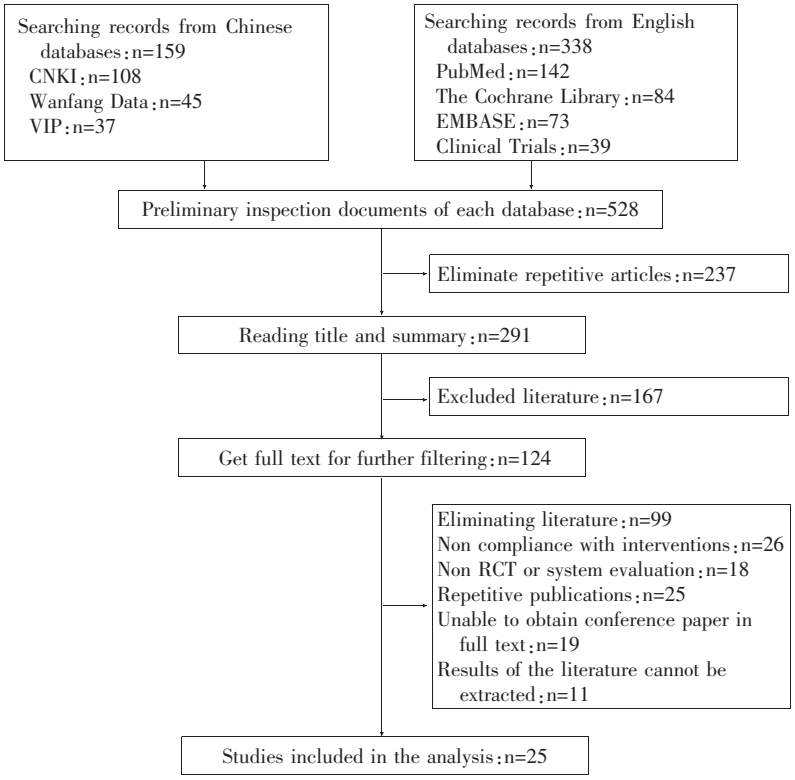

Figure 1 Flow chart of the systematic literature search and selection

1.4.3 证据质量评价

采用 GRADE 系统[10]对结局指标进行证据质量分级,并对其进行亚组分析,以评估对效应估计值正确的把握程度。随机对照试验被预设为“高级”证据,根据降低证据质量的因素,如局限性[11]、不一致性[12]、不间接性[13]、不精确性[14]和发表偏倚[15]等,进行降级处理,其中降 1 级为“中级”,降 2 级为“低级”,降 3 级为“极低级”。

2 结 果

2.1 文献筛选流程及结果

初检共获得相关文献 528 篇,经逐层筛选,最后纳入 25 个 SR/Meta 分析。文献检索和筛选流程见图1(Figure 1)。

2.2 纳入研究的基本特征

纳入的 25 篇 SR/Meta 分析有 11 篇英文文献和 14 篇中文文献,纳入原始研究类型均为 RCT。纳入原始研究数量为 3~44 篇;样本量为 695~4 664。治疗组干预措施以 PD-1/PD-L1 单药治疗或联合化疗为主,对照组以环磷酰胺化疗或多西他赛化疗为主。25 个 SR/Meta 分析对纳入的 RCT 方法学质量评价,有 7 个[7,16,18,25-26,30,38]采用的是 Jadad 量表,12 个[17,19,23,27-29,31-33,36-37]采用的是 Cochrane 系统推荐的偏倚风险评估工具,有 6 个[6,20-22,24,34]未具体说明方法。纳入研究的基本特征见表 2(Table 2)。

2.3 主要结局指标

2.3.1 评价疗效指标

所纳入文献系统合并分析了 PD-1/PD-L1 抑制剂或联合化疗的 ORR、OS 和 PFS,结果显示 PD-1/PD-L1 抑制剂或联合常规治疗的 ORR、OS 和 PFS 优于单用化疗。其中,24 篇文献[6-7,16-24,26-38]报道 PD-1/PD-L1 抑制剂显著提高晚期 NSCLC 治疗的 OS;15 篇文献[6-7,17-19,22-23,27,29,31,34-38]报

Table 2 The characteristics of included studies

Articles	Author(Year)	Quality assessment	Cancer type	Regimen comparison	Number of RCT	Sample size	OS	PFS	ORR
Meta analysis	Landre(2020)[6]	Unclear	NSCLC	Anti-PD-(L)1 + CTX *vs* CTX	8	2037	HR=0.75; 95%CI:0.63~0.89; *P*=0.0008	HR=0.72; 95%CI:0.65~0.80; *P*<0.0001	OR=2.06; 95%CI:1.50~2.83; *P*<0.0001
Meta analysis	Tartarone (2019)[16]	Jadad scale	NSCLC	Anti-PD-1 *vs* CTX	7	4664	HR=0.72; 95%CI:0.67~0.78; *P*<0.0001	HR=0.88; 95%CI:0.78~0.99; *P*=0.027	–
Meta analysis	Khan(2018)[17]	Cochrane Risk of Bias Tool	NSCLC	Anti-PD-(L)1 *vs* CTX	7	3867	HR=0.72; 95%CI:0.63~0.82; *P*<0.00001	HR=0.84; 95%CI:0.72~0.97; *P*<0.02	OR=1.52; 95%CI:1.08~2.14; *P*<0.02
Meta analysis	Zhao(2018)[18]	Jadad scale	NSCLC	Anti-PD-(L)1 *vs* CTX	5	3025	HR=0.69; 95%CI:0.63~0.75; *P*<0.0001	HR=0.87; 95%CI:0.81~0.94; *P*=0.0004	RR=1.53; 95%CI:1.16~2.01; *P*=0.003
Meta analysis	Zhou(2018)[19]	Cochrane Risk of Bias Tool	NSCLC	Anti-PD-(L)1+ CTX *vs* CTX	6	3144	HR=0.68; 95%CI:0.53~0.87; *P*=0.002	HR=0.62; 95%CI:0.57~0.67; *P*<0.001	RR=1.56; 95%CI:1.29~1.89; *P*<0.001
Meta analysis	Lee(2018)[20]	Unclear	NSCLC	Anti-PD-(L)1 *vs* CTX	5	3025	HR=0.69; 95%CI:0.63~0.75; *P*<0.001	–	–
Meta analysis	Jiang(2017)[21]	Unclear	NSCLC	Anti-PD-(L)1 *vs* CTX	5	3025	HR=0.70; 95%CI:0.63~0.77; *P*<0.001	HR=0.86; 95%CI:0.77~0.97; *P*=0.02	–
Meta analysis	Pilotto(2018)[22]	Unclear	NSCLC	Pembrolizumab + CTX *vs* CTX	4	2754	HR=0.50; 95%CI:0.35~0.72; *P*=0.001	HR=0.36; 95%CI:0.26~0.48; *P*<0.001	OR=5.35; 95%CI:2.77~10.34; *P*<0.001
				Pembrolizumab *vs* CTX			HR=0.67; 95%CI:0.56~0.79; *P*=0.001	HR=0.65; 95%CI:0.40~1.05; *P*=0.081	OR=1.58; 95%CI:1.13~2.21; *P*=0.007
Meta analysis	Peng(2017)[23]	Cochrane Risk of Bias Tool	NSCLC	Pembrolizumab/nivolumab *vs* docetaxel	3	1887	HR=0.67; 95%CI:0.60~0.75; *P*<0.00001	HR=0.81; 95%CI:0.70~0.94; *P*=0.006	OR=2.02; 95%CI:1.52~2.68; *P*<0.00001
Meta analysis	Lee(2017)[24]	Unclear	NSCLC	Anti-PD-(L)1 *vs* CTX	3	1903	HR=0.68; 95%CI:0.61~0.77; *P*<0.0001	–	–
Meta analysis	Zhou(2016)[7]	Jadad scale	NSCLC	Anti-PD-(L)1 *vs* CTX	3	1141	HR=0.71; 95%CI:0.61~0.81; *P*<0.001	HR=0.83; 95%CI:0.65~1.06; *P*=0.134	OR=1.05; 95%CI:1.08~2.07; *P*=0.015
Meta analysis	Su(2016)[25]	Jadad scale	NSCLC	Anti-PD-(L)1 *vs* CTX	4	2392	–	–	–
Meta analysis	Fu(2019)[26]	Jadad scale	NSCLC	Anti-PD-(L)1 *vs* CTX	4	2737	HR=0.69; 95%CI:0.63~0.75; *P*<0.00001	HR=0.85; 95%CI:0.75~0.96; *P*<0.00001	–

Notes: HR: hazard ratio; OR: odds ratio; RR: risk ratio; RD: risk difference; –: missing data

Table 2 The characteristics of included studies(continued)

Articles	Author(Year)	Quality assessment	Cancer type	Regimen comparison	Number of RCT	Sample size	OS	PFS	ORR
Meta analysis	Wei(2019)[27]	Cochrane Risk of Bias Tool	NSCLC	Anti-PD-(L)1 *vs* docetaxel	7	4101	HR=0.65; 95%CI:0.65~0.92; *P*=0.02	HR=0.59; 95%CI:0.59~0.70; *P*<0.00001	RR=1.72; 95%CI:1.13~2.62; *P*=0.01
Meta analysis	Huo(2020)[28]	Cochrane Risk of Bias Tool	NSCLC	Anti-PD-(L)1 + docetaxel *vs* docetaxel	6	3238	HR=8.06; 95%CI:0.79~0.94; *P*=0.0006	HR=0.81; 95%CI:0.78~0.84; *P*<0.00001	–
Meta analysis	Jiang(2020)[29]	Cochrane Risk of Bias Tool	NSCLC	Anti-PD-(L)1 + docetaxel *vs* docetaxel	7	3945	HR=0.66; 95%CI:0.61~0.72; *P*<0.00001	HR=0.72; 95%CI:0.59~0.87; *P*=0.0007	OR=0.32; 95%CI:0.25~0.40; *P*<0.00001
Meta analysis	Song(2018)[30]	Jadad scale	NSCLC	Middle-young aged:anti-PD-(L)1 *vs* docetaxel The aged:anti-PD-(L)1 *vs* docetaxel	6	3277	HR=0.76; 95%CI:0.60~0.97; *P*=0.01	HR=0.77; 95%CI:0.60~0.97; *P*=0.03	–
Meta analysis	Wan(2018)[31]	Cochrane Risk of Bias Tool	NSCLC	Anti-PD-(L)1 *vs* docetaxel	4	1991	HR=0.70; 95%CI:0.62~0.80; *P*<0.00001	HR=0.75; 95%CI:0.67~0.85; *P*<0.00001	RR=1.31; 95%CI:1.05~1.62; *P*=0.01
Meta analysis	Zhang(2019)[32]	Cochrane Risk of Bias Tool	NSCLC	Anti-PD-(L)1 + docetaxel *vs* docetaxel	5	1467	HR=0.51; 95%CI:0.41~0.65; *P*=0.57	HR=0.52; 95%CI:0.43~0.63; *P*=0.89	OR=3.64; 95%CI:2.56~5.16; *P*=0.46
Meta analysis	Wang(2020)[33]	Cochrane Risk of Bias Tool	NSCLC	Pembrolizumab/nivolumab *vs* docetaxel	4	2299	HR=0.67; 95%CI:0.61~0.74; *P*<0.01	HR=0.80; 95%CI:0.73~0.88; *P*<0.01	–
Meta analysis	Feng(2018)[34]	Unclear	NSCLC	Anti-PD-(L)1 *vs* CTX	44	695	RD=0.54; 95%CI:0.46~0.63; *P*<0.00001	RD=0.27; 95%CI:0.20~0.33; *P*<0.00001	RD=0.22; 95%CI:0.20~0.25; *P*<0.00001
Meta analysis	Wang(2016)[35]	Jadad scale	NSCLC	Anti-PD-(L)1 *vs* docetaxel	4	1781	HR=0.61; 95%CI:0.61~0.75; *P*<0.05	HR=0.38; 95%CI:0.69~1.74; *P*>0.05	HR=0.56; 95%CI:0.43~0.73; *P*<0.05
Meta analysis	Zhou(2018)[36]	Cochrane Risk of Bias Tool	NSCLC	Anti-PD-(L)1 *vs* docetaxel	6	2556	HR=0.68; 95%CI:0.61~0.75; *P*<0.00001	–	RR=1.81; 95%CI:1.40~2.33; *P*<0.00001
Meta analysis	Chen(2018)[37]	Cochrane Risk of Bias Tool	NSCLC	Anti-PD-(L)1 *vs* CTX	8	4207	HR=0.72; 95%CI:0.66~0.78; *P*<0.00001	HR=0.83; 95%CI:0.72~0.97; *P*=0.02	RR=1.03; 95%CI:1.02~1.67; *P*=0.04
Meta analysis	Ding(2019)[38]	Cochrane Risk of Bias Tool	NSCLC	Anti-PD-(L)1 *vs* CTX	7	3277	HR=0.71; 95%CI:0.58~0.87; *P*=0.00007	HR=0.62; 95%CI:0.57~0.67; *P*<0.00001	RR=1.56; 95%CI:1.35~1.79; *P*<0.00001

Notes:HR:hazard ratio;OR:odds ratio;RR:risk ratio;RD:risk difference;–:missing data

道 PD-1/PD-L1 抑制剂可提高晚期 NSCLC 治疗的 ORR，其中，有 2 篇文献报道 PD-1/PD-L1 抑制剂可提高 ORR，但疗效不显著（OR=1.52，95%CI：1.08~2.14，*P*<0.02[17]；OR=1.05，95%CI：1.08~2.07，*P*=0.015[7]）；另外，有 1 篇文献[32]提示差异无统计学意义；18 篇文献[6,16-19,21-23,26-31,33-34,37-38]报道 PD-1/PD-L1 抑制剂能够延长患者的 PFS，其中，有 5 篇文献[16-17,21,30,37]提示 PD-1/PD-L1 抑制剂可延长患者的 PFS，但疗效不显著（HR=0.88，95%CI：0.78~0.99，*P*=0.027 [16]；HR=0.86，95%CI：0.77~0.97，*P*=0.02[21]；HR=0.84，95%CI：0.72~0.97，*P*<0.02[17]；HR=0.77，95%CI：0.60~0.97，*P*=0.03[30]；HR=0.83，95%CI：0.72~0.97，*P*=0.02[37]），除此之外，3 篇文献[7,32,35]提示 PFS 差异无统计学意义。值得注意的是，Pilotto 等[22]的亚组研究结果显示，帕博利珠单抗联合环磷酰胺较单独使用环磷酰胺可显著提高 ORR（HR=0.36，95%CI：0.26~0.48，*P*<0.001），而单用帕博利珠单抗和单用环磷酰胺在提高 ORR 方面差异无统计学意义（HR=0.65，95%CI：0.40~1.05，*P*=0.081）。

2.3.2 评价不良反应指标

16 篇文献[7,16-19,23,25-26,29,31-37]报道了 PD-1/PD-L1 抑制剂的相关不良事件，指出 PD-1/PD-L1 抑制剂相对于化疗，不良事件发生率显著降低，其中 11 篇文献[7,16-19,31-35]报道了 PD-1/PD-L1 抑制剂存在 3 级以上(包括 3 级)不良事件，5 篇文献[7,19,23,31,33]报道了 PD-1/PD-L1 抑制剂存在甲状腺功能减退、甲亢、皮疹、肺炎等不良反应。

2.4 纳入研究的质量评价

2.4.1 文献报告质量评价

运用 PRIMSA 条目对纳入的 SR/Meta 分析进行质量评价(Table 3)。参照 PRIMSA 条目，25 篇文献均对结构式摘要、理论基础、目的、信息来源、检索、资料提取、结果综合、研究选择、研究特征、单个研究结果、证据总结、结论有描述；所有文献均未提及方案和注册；对标题(22/25)，方法部分的纳入标准(23/25)、研究选择(7/25)、资料提取(11/25)、资料条目(20/25)、单个研究存在的偏倚(21/25)、概括效应指标(23/25)、研究偏倚(14/25)、其他分析(14/25)等部分提及；结果部分的研究内部偏倚风险(20/25)、结果的综合(23/25)、研究间偏倚(14/25)、其他分析(18/25)以及局限性

Table 3 Quality assessment by PRISMAs for included systematic reviews or Meta analyses

Section	PRISMA entry	Item	Complete report		Partially reported+not reported	
			Number of articles	Proportion (%)	Number of articles	Proportion (%)
Title	1	Title	22	88	3	12
Abstract	2	Structured summary	25	100	0	0
Introduction	3	Rationale	25	100	0	0
	4	Objectives	25	100	0	0
Methods	5	Protocol and registration	0	0	25	100
	6	Eligibility criteria	23	92	2	8
	7	Information sources	25	100	0	0
	8	Search	25	100	0	0
	9	Study selection	7	28	18	72
	10	Data collection process	22	88	3	12
	11	Data items	20	80	5	20
	12	Risk of bias in individual studies	21	84	4	16
	13	Summary measures	23	92	2	8
	14	Synthesis of results	24	96	1	4
	15	Risk of bias across studies	14	56	11	44
	16	Additional analyses	14	56	11	44
Results	17	Study selection	25	100	0	0
	18	Study characteristics	25	100	0	0
	19	Risk of bias within studies	20	80	5	20
	20	Results of individual studies	23	92	2	8
	21	Synthesis of results	23	92	2	8
	22	Risk of bias across studies	14	56	11	44
	23	Additional analysis	18	72	7	28
Discussion	24	Summary of evidence	25	100	0	0
	25	Limitations	18	72	7	28
	26	Conclusions	25	100	0	0
Funding	27	Funding	10	40	15	60

(18/25)和资金(10/25)等描述不够全面。

2.4.2 方法学质量评价结果

关键条目的符合情况如下：条目2、4、7均为0(0/25)，存在极大缺陷；条目9为56%(14/25)，条目11为48%(12/25)，条目13为48%(12/25)，条目15为48%(12/25)，存在较大缺陷。根据AMSTAR 2方法学质量等级评价标准，纳入的25篇SR/Meta分析均不满足关键条目2、4、7，故均为极低质量(Table 4)。

2.4.3 证据质量评价结果

采用GRADE系统分级对ORR、OS、PFS等36个结局指标进行证据质量评价，并对其进行亚组分析(Table 5)，结果显示SR/Meta分析结局指标的等级以低质量和中质量为主，3项为高质量，43项为中等质量，87项为低质量，22项为极低质量，导致降级的最主要因素为发表偏倚，其次为局限性，以及不一致性。研究的发表偏倚降级提示纳入研究数量少且结果多为阳性，或者存在纳入研究漏斗图不对称等问题；局限性降级提示SR/Meta分析纳入的RCT在随机、分配隐藏和盲法等研究设计方面仍存在一定缺陷；不一致性降级提示不同研究可信区间的重叠程度较差，异质性大。

3 讨 论

SR/Meta分析在医疗卫生领域中作用日益突出，高质量的系统评价已成为临床科研工作者及决策者制定临床方案和选择治疗措施的重要依据，然而目前国内外SR/Meta分析的总体报告质量普遍较低[39]。系统评价再评价作为一种综合评价体系和研究方法，在现代循证医学发展中具有巨大优势。本研究分别采用PRISMA声明、AMSTAR 2工具和GRADE方法对PD-1治疗晚期非小细胞肺癌的SR/Meta分析进行再评价，旨在倡导临床科研工作者重视并严格遵循SR/Meta分析的报告规范，提高报告质量，为PD-1/PD-L1治疗肺癌提供更可靠的循证医学证据。

在报告质量方面，PRISMA声明结果显示，27个条目中有12个条目（条目2、3、4、7、8、10、14、17、18、20、24、26）所有文献都进行了全面描述；而条目5(方案和注册)所有文献均未提及。15个条目(条目1、6、9、10、11、12、13、15、16、19、21、22、23、25、27)描述的不够全面，其中描述最少的条目为研究选择，只有7篇文献进行完整报告；其次是资金、研究偏倚、研究间偏倚、方法部分的其他分析，也只有不到15篇文献进行完整报告。以上结果显示，纳入研究多数存在一定的报告缺陷。

在方法学质量方面，AMSTAR 2量表评价结果显示，所有条目中，只有条目1(研究的问题和纳入标准包含PICO)被评定为报告完整(100%)。有17篇[17,19,21,23,25-34,36-38]解释了纳入的研究设计类型，20篇[6,7,16-19,21,23,25-28,30-34,36-38]采用合理的研究筛选方式，20篇[6,7,16,18,19,20-21,23-28,30-34,36,38]采用合理的数据提取方式，14篇[16,18,23,25-29,31-33,36-38]考虑了纳入研究的偏倚风险，12篇[7,16-18,20-21,24,27,30-32,37]采用了合适的统计方法合并结果，2篇[16,28]在结果中说明了纳入研究的偏倚风险对研究结果的影响，12篇[17,18,20,28,30-31,33-38]在讨论中说明了偏倚风险对研究结果的影响，10篇[7,18-20,24,27,30,32,36-37]在讨论中合理地解释异质性，12篇[7,18-21,25,27-28,30-31,34,37]分析了发表偏倚，9篇文献[6,16-23]报告了潜在的利益冲突。25篇SR/Meta分析均存在关键条目2、4、7缺失：所有SR/Meta分析均未提前注册，缺乏如PROSPERO、Cochrane等严格完善的系统评价质量保证系统，可能会影响系统评价制定的规范性和严谨性；25篇SR/Meta分析文献检索均不全面，主要原因源自未对临床试验注册平台、参考文献等进行检索或限制了纳入研究文献的语种但未说明理由，会造成一定的发表偏倚；未提供排除文献的清单和具体理由，这可能与目前大多学术刊物上版面限制有关，导致研究可能存在一定的选择性偏倚。非关键条目8、10缺失：所有SR/Meta分析均未详细描述纳入研究，不利于研究者判断纳入的研究是否恰当以及研究间是否存在临床异质性；未报告纳入研究的基金来源，无法准确判断是否存在潜在利益冲突导致影响结果客观性。以上结果显示，纳入的SR/Meta分析总体方法学质量仍有待提高。

本次再评价结果显示，PD-1/PD-L1或联合化疗相比单纯化疗显著提高患者的生存率和延长患者的生存期，且在不良事件方面，相对化疗而言，免疫治疗的不良事件发生率低，因此对于晚期NSCLC PD-1/PD-L1显示出良好的治疗效果和安全性。但目前相关的SR/Meta分析方法学质量不高，或原始研究方法学等方面存在一定的缺陷，使得结局指标的论

Table 4 Methodological quality assessment of included SR/Meta analyses

Reviews	Item1	Item2	Item3	Item4	Item5	Item6	Item7	Item8	Item9	Item10	Item11	Item12	Item13	Item14	Item15	Item16
Peng(2017)[23]	Y	N	Y	PY	Y	Y	N	PY	Y	N	N	N	N	N	N	Y
Jiang(2017)[21]	Y	N	Y	PY	Y	Y	N	PY	N	N	Y	N	N	N	Y	Y
Zhou(2018)[19]	Y	N	Y	PY	Y	Y	N	PY	N	N	N	N	N	N	Y	Y
Landre(2020)[6]	Y	N	N	PY	Y	Y	PY	PY	N	N	N	N	N	N	N	Y
Khan(2018)[17]	Y	N	Y	PY	Y	N	N	PY	PY	N	Y	N	Y	Y	N	Y
Tartarone(2018)[16]	Y	N	N	PY	Y	Y	N	PY	Y	N	Y	Y	N	N	N	Y
Zhou(2016)[7]	Y	N	N	PY	Y	Y	N	PY	N	N	Y	N	N	Y	Y	N
Zhao(2018)[18]	Y	N	N	PY	Y	Y	N	PY	Y	N	Y	N	Y	Y	Y	Y
Pilotto(2018)[22]	Y	N	N	PY	N	N	N	PY	N	N	N	N	N	N	N	Y
Lee(2017)[24]	Y	N	N	PY	N	Y	N	PY	N	N	Y	N	N	Y	N	N
Lee(2018)[20]	Y	N	N	PY	N	Y	N	PY	N	N	Y	N	Y	Y	Y	Y
Su(2016)[25]	Y	N	Y	PY	Y	Y	N	PY	Y	N	N	N	N	N	Y	N
Fu(2019)[26]	Y	N	Y	PY	Y	Y	N	PY	Y	N	N	N	N	N	N	N
Wei(2019)[27]	Y	N	Y	PY	Y	Y	N	PY	Y	N	Y	N	N	Y	Y	N
Huo(2020)[28]	Y	N	Y	PY	Y	Y	N	PY	Y	N	N	Y	Y	N	Y	N
Jiang(2020)[29]	Y	N	Y	PY	N	N	N	PY	Y	N	N	N	N	N	N	N
Song(2018)[30]	Y	N	Y	PY	Y	Y	N	PY	PY	N	Y	N	Y	Y	Y	N
Wan(2018)[31]	Y	N	Y	PY	Y	Y	N	PY	Y	N	Y	N	Y	N	Y	N
Zhang(2019)[32]	Y	N	Y	PY	Y	Y	N	PY	Y	N	Y	N	N	Y	N	N
Wang(2020)[33]	Y	N	Y	PY	Y	Y	N	PY	Y	N	N	N	Y	N	N	N
Feng(2018)[34]	Y	N	Y	PY	Y	Y	N	PY	N	N	N	N	Y	N	Y	N
Wang(2016)[35]	Y	N	N	PY	N	N	N	PY	N	N	N	N	Y	N	N	N
Zhou(2018)[36]	Y	N	Y	PY	Y	Y	N	PY	Y	N	N	N	Y	Y	N	N
Chen(2018)[37]	Y	N	Y	PY	Y	N	N	PY	Y	N	Y	N	Y	Y	Y	N
Ding(2019)[38]	Y	N	Y	PY	Y	Y	N	PY	Y	N	N	N	Y	N	N	N

Notes: Y: yes; PY: partial yes; N: not; Item 1: Did the research questions and inclusion criteria for the review include the components of PICO? Item 2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? Item 3: Did the review authors explain their selection of the study designs for inclusion in the review? Item 4: Did the review authors use a comprehensive literature search strategy? Item 5: Did the review authors perform study selection in duplicate? Item 6: Did the review authors perform data extraction in duplicate? Item 7: Did the review authors provide a list of excluded studies and justify the exclusions? Item 8: Did the review authors describe the included studies in adequate detail? Item 9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? Item 10: Did the review authors report on the sources of funding for the studies included in the review? Item 11: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? Item 12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Item 13: Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? Item 14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? Item 15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? Item 16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Table 5 Quality assessment of GRADEs of included SR/Meta analyses

Reviews	Outcome indicators (number of studies)	Subgroup (number of studies)	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
Peng(2017)[23]	Overall response rates(4)	Pembrolizumab *vs* docetaxel(2)	−1	0	0	0	−1	Low
		Nivolumab *vs* docetaxel(2)	−1	0	0	0	−1	Low
	Overall survival(4)	Pembrolizumab *vs* docetaxel(2)	−1	0	0	0	−1	Low
		Nivolumab *vs* docetaxel(2)	−1	0	0	0	−1	Low
	Progression-free survival(4)	Pembrolizumab *vs* docetaxel(2)	−1	0	0	0	−1	Low
		Nivolumab *vs* docetaxel(2)	−1	0	0	0	−1	Low
	Adverse events(4)	Decreased appetite(4)	−1	0	0	0	−1	Low
		Fatigue(4)	−1	0	0	0	−1	Low
		Nausoa(4)	−1	0	0	0	−1	Low
		Asthenia(4)	−1	0	0	0	−1	Low
		Diarrhea(4)	−1	0	0	0	−1	Low
		Anemia(4)	−1	0	0	0	−1	Low
		Alopecia(4)	−1	0	0	0	−1	Low
		Neutropenia(4)	−1	0	0	0	−1	Low
		Pneumonitis(4)	−1	0	0	0	−1	Low
		Hypothyroidism(4)	−1	0	0	0	−1	Low
Jiang(2017)[21]	Progression-free survival(5)		−1	0	0	0	−1	Moderate
	Overall survival(5)		−1	0	0	0	−1	Low
Zhou(2018)[19]	Progression-free survival(6)		−1	0	0	0	0	Moderate
		PD-L1<1%(5)	−1	0	0	0	0	Moderate
		PD-L1 1%~49%(4)	−1	0	0	0	−1	Low
		PD-L1≥50%(4)	−1	0	0	0	−1	Low
	Overall survival(5)		−1	−1	0	0	0	Low
	Objective response rate(6)		−1	−1	0	0	0	Low
	Treatment-related adverse events(5)	Any grade(6)	−1	−1	0	0	0	Low
		Grade 3,4,5(6)	−1	0	0	0	0	Moderate
		Led to discontinution(5)	−1	0	0	0	0	Moderate
		Serious adverse events(3)	−1	0	0	0	−1	Low
		Led to death(6)	−1	0	0	0	0	Moderate
	Immune mediated adverse events	Any grade(4)	−1	0	0	0	−1	Low
		Grade 3,4,5(5)	−1	0	0	0	0	Moderate
		Led to death(5)	−1	0	0	0	0	Moderate
Landre(2020)[6]	Overall survival(4)		−1	0	0	0	−1	Low
	Progression-free survival(7)	Pembrolizumab(2)	−1	0	0	0	−1	Low

Table 5 Quality assessment of GRADEs of included SR/Meta analyses(continued)

Reviews	Outcome indicators (number of studies)	Subgroup (number of studies)	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
		Atezolizumab(2)	−1	0	0	0	−1	Low
		Nivolumab(1)	−1	0	0	0	−1	Low
	Objective response rate(7)		−1	0	0	0	0	Moderate
Khan(2018)[17]	Overall survival(8)		−1	−1	0	0	0	Low
	Progression-free survival(8)		−1	−1	0	0	0	Low
	Objective response rate (8)		−1	−1	0	0	0	Low
	Treatment related adverse events(8)	Overall treatment related adverse events(8)	−1	0	0	0	0	Moderate
		Grade 3,4,5 treatment related adverse events(8)	−1	−1	0	0	0	Low
Tartarone(2019)[16]	Overall survival(8)	PD-1(5)	0	0	0	0	0	Moderate
		PD-L1(3)	0	0	0	0	−1	Low
	Progression-free survival(8)	PD-1(5)	0	0	0	0	0	Moderate
		PD-L1(3)	0	0	0	0	−1	Low
	Grade 3~4 adverse events(8)	PD-1(5)	0	−1	0	0	0	Low
		PD-L1(3)	0	−1	0	0	−1	Critically low
Zhou(2016)[7]	Overall survival(3)	>1%(3)						
		>5%(3)						
		>10%(3)	0	0	0	0	−1	Moderate
		<1%(3)						
		<5%(2)						
		<10%(2)						
	Progression-free survival(3)	>1%(3)						
		>5%(3)						
		>10%(3)	0	0	0	0	−1	Moderate
		<1%(3)						
		<5%(2)						
		<10%(2)						
	Grade 3~4 adverse events(3)		0	0	0	0	−1	Moderate
	Overall response rate(3)		0	0	0	0	−1	Low
	Adverse events(2)							
		Fatigue(2)	0	0	0	0	−1	Moderate
		Nausea(2)	0	0	0	0	−1	Moderate
		Decreased appetite(2)	0	0	0	0	−1	Moderate
		Asthenia(2)	0	0	0	0	−1	Moderate

Table 5 Quality assessment of GRADEs of included SR/Meta analyses(continued)

Reviews	Outcome indicators (number of studies)	Subgroup (number of studies)	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
		Diarrhea(2)	0	0	0	0	−1	Moderate
		Myalgia(2)	0	0	0	0	−1	Moderate
		Anemia(2)	0	0	0	0	−1	Moderate
		Alopecia(2)	0	0	0	0	−1	Moderate
		Neutropenia(2)	0	0	0	0	−1	Moderate
		Pneumonitia(2)	0	0	0	0	−1	Moderate
		Hypothyroidism(2)	0	0	0	0	−1	Moderate
Zhao(2018)[18]	Overall survival rate(6)		0	0	0	0	0	High
		PD-L1<1%(4)	0	0	0	0	−1	Moderate
		PD-L1≥1%(6)	0	0	0	0	0	High
		PD-L1≥5%(4)	0	0	0	0	−1	Moderate
		PD-L1≥10%(4)	0	0	0	0	−1	Moderate
	Progression-free survival(6)		0	0	0	0	0	Low
	Proportion of patients with an objective response rate(6)		0	−1	0	0	0	Low
	Grade 3~5 adverse events(6)		0	−1	0	0	0	Low
Pilotto(2018)[22]	Overall survival(4)	Add-On(2)	−1	−	0	−1	−1	Critically low
		Head-to-Head(2)	−1	−	0	0	−1	Low
	Progression-free survival(4)	Add-On(2)	−1	−	0	−1	−1	Critically low
		Head-to-Head(2)	−1	−	0	0	−1	Low
	Overall response rate(3)	Add-On(2)	−1	−	0	−1	−1	Critically low
		Head-to-Head(2)	−1	−	0	0	−1	Low
Lee(2017)[24]	Overall survival(6)	*EGFR* wild-type(3)	−1	0	0	0	−1	Low
		EGFR mutated(3)	−1	0	0	0	−1	Low
Lee(2018)[20]	Overall survival(8)	*EGFR* wild-type(4)	−1	0	0	0	−1	Low
		EGFR mutated(4)	−1	0	0	0	−1	Low
	Overall survival(6)	*KRAS* wild-type(3)	−1	0	0	0	−1	Low
		KRAS mutated(3)	−1	0	0	0	−1	Low
Su(2016)[25]	Overall response rate(5)		−1	0	0	0	0	Moderate
	Adverse events(5)		−1	−1	0	0	0	Low
Fu(2019)[26]	Overall survival(5)		−1	0	0	0	0	Moderate
	Progression-free survival(5)		−1	−1	0	0	0	Low
	Treatment related adverse events(5)		−1	−1	0	0	0	Low

Note: − : missing data

Table 5 Quality assessment of GRADEs of included SR/Meta analyses(continued)

Reviews	Outcome indicators (number of studies)	Subgroup (number of studies)	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
	Progression-free survival	Anti-PD-(L)1 *vs* docetaxel(4)	−1	−1	0	0	−1	Critically low
	Overall survival	Anti-PD-(L)1 *vs* docetaxel(3)	−1	−1	0	0	−1	Critically low
	Overall response rate	Anti-PD-(L)1 *vs* docetaxel(2)	−1	−1	0	0	−1	Critically low
Huo(2020)[28]	Overall survival(6)		0	−1	0	0	0	Moderate
	Progression-free survival(6)		0	0	0	0	0	High
Jiang(2020)[29]	Overall survival(7)		−1	0	0	0	0	Moderate
	Progression-free survival(6)		−1	−1	0	0	0	Low
	Overall response rate(7)		−1	−1	0	0	0	Low
	Overall adverse events(7)		−1	0	0	0	0	Moderate
	Grade 3~5 adverse events(7)		−1	−1	0	0	0	Low
Song(2018)[30]	Middle-young aged overall survival	First-line anti-PD-(L)1 *vs* docetaxel	0	−1	0	0	0	Moderate
		Second-line anti- PD-(L)1 *vs* docetaxel	0	0	0	0	−1	Moderate
	The aged overall survival	First-line anti- PD-(L)1 *vs* docetaxel	0	−1	0	0	0	Moderate
		Second-line anti- PD-(L)1 *vs* docetaxel	0	0	0	0	0	Critically low
Wan(2018)[31]	Overall survival(4)		−1	0	0	0	−1	Low
	Overall response rate(4)		−1	0	0	0	−1	Low
	Progression-free survival(4)	PD-L1 ⩾1%(4)	−1	0	0	0	−1	Low
		PD-L1 ⩾5%(4)	−1	−1	0	0	−1	Critically low
		PD-L1 ⩾10%(4)	−1	0	0	0	−1	Low
		PD-L1 <1%(4)	−1	−1	0	0	−1	Critically low
		PD-L1 <5%(2)	−1	−1	0	0	−1	Critically low
		PD-l1 <10%(2)	−1	−1	0	0	−1	Critically low
	Grade 3~5 adverse events	Fatigue(4)	−1	−1	0	0	−1	Critically low
		Nausea(4)	−1	−1	0	0	−1	Critically low
		Decreased appetite(4)	−1	0	0	0	−1	Low
		Asthenia(4)	−1	0	0	0	−1	Low
		Diarrhea(4)	−1	0	0	0	−1	Low
		Myalgia(4)	−1	0	0	0	−1	Low
		Anemia(4)	−1	0	0	0	−1	Low
		Neutropenia(4)	−1	0	0	0	−1	Low
		Pneumonitia(3)	−1	0	0	0	−1	Low
		Hypothyroidism(3)	−1	0	0	0	−1	Low
Zhang(2019)[32]	Overall survival(2)		−1	0	0	0	−1	Low
	Progression-free survival(2)		−1	0	0	0	−1	Low
	Overall response rate(2)		−1	0	0	0	−1	Low
	Grade 3~5 adverse events(2)		−1	0	0	0	−1	Low

Table 5 Quality assessment of GRADEs of included SR/Meta analyses(continued)

Reviews	Outcome indicators (number of studies)	Subgroup (number of studies)	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
Wang(2020)[33]	Overall survival(4)		−1	0	0	0	−1	Low
	Progression-free survival(3)		−1	0	0	0	−1	Low
	Overall adverse events(4)		−1	0	0	0	−1	Low
	Grade 3~5 adverse events(4)		−1	−1	0	0	−1	Critically low
Feng(2018)[34]	Overall response rate	Overall therapy(43)	−1	−1	0	0	−1	Critically low
		First-line combined therapy(6)	−1	−1	0	0	0	Low
		First-line single therapy(9)	−1	0	0	0	0	Moderate
	Overall adverse events(18)		−1	−1	0	0	0	Low
	Grade 3~5 adverse events(25)		−1	−1	0	0	0	Low
Wang(2016)[35]	Median overall survival(4)		−1	0	0	0	−1	Low
	Overall response rate(4)		−1	0	0	0	−1	Low
	Median progression-free survival(4)		−1	−1	0	0	−1	Critically low
	Overall adverse events(4)		−1	−1	0	0	−1	Critically low
	Grade 3~5 adverse events(4)		−1	−1	0	0	−1	Critically low
Zhou(2018)[36]	Median overall survival(4)		−1	0	0	0	−1	Low
	Overall response rate(3)		−1	0	0	0	−1	Low
	Overall adverse events(6)		−1	−1	0	0	0	Low
Chen(2018)[37]	Overall response rate(7)		−1	−1	0	0	0	Low
	Progression-free survival(7)		−1	−1	0	0	0	Low
	Overall survival(7)		−1	0	0	0	0	Moderate
	Treatment related adverse events(7)		−1	−1	0	0	0	Low
Ding(2019)[38]	Progression-free survival(7)		−1	0	0	0	0	Moderate
		PD-L1 <1%(6)	−1	0	0	0	0	Moderate
		PD-L1 1%~49%(5)	−1	0	0	0	0	Moderate
		PD-L1≥50%(5)	−1	0	0	0	0	Moderate
	Overall survival(7)		−1	−1	0	0	0	Low
	Overall response rate(7)		−1	−1	0	0	0	Low
		PD-L1 <1%(4)	−1	−1	0	0	−1	Critically low
		PD-L1 1%~49%(3)	−1	−1	0	0	−1	Critically low
		PD-L1≥50%(3)	−1	−1	0	0	−1	Critically low
		PD-1 drug(4)	−1	−1	0	0	−1	Critically low
		PD-L1 drug(3)	−1	0	0	0	−1	Low

证强度降低。再评价结果显示影响证据强度的最主要因素为研究的发表偏倚，说明纳入研究数量少且结果多为阳性，或存在纳入研究漏斗图不对称等问题。

结局指标评价是当前全球医疗领域研究关注的重点，合理的疗效评定指标是临床试验的关键环节，甚至会对结论产生决定性的影响[40]。纳入的25篇文献中，仅2篇文献[20,24]报道PD-1/PD-L1抑制剂显著提高*EGFR*野生型的OS，1篇文献[20]报道PD-1/PD-L1抑制剂显著提高*KRAS*突变型的OS。目前PD-1/PD-L1抑制剂在晚期NSCLC治疗方面显示出巨大的潜力[41-42]，但单药治疗的获益人群较低[43]，因此筛选出免疫治疗获益人群显得尤为重要。因此，要证实PD-1/PD-L1抑制剂或联合化疗治疗晚期NSCLC的有效性，不仅要观察ORR、OS、PFS等评价疗效的指标，未来的临床试验还应关注EGFR、KRAS等其他指标，才能科学地评价PD-1/PD-L1或联合化疗对晚期NSCLC患者的最终益处。因此，在今后的科研过程中，需要遵循科学范式，合理选择评价指标，根据需要赋予不同结局指标权重，形成一套系统、规范、合理的指标体系。

本研究仍存在一定的局限性，纳入的SR/Meta分析数量有限，且质量偏低，可能降低研究结果的准确性。其次，未检索中英文除外的文献及相关灰色文献，可能降低了查全率。

综上，目前PD-1/PD-L1或联合化疗治疗晚期NSCLC的SR/Meta分析整体方法学质量水平不高，证据强度偏低，降低了PD-1/PD-L1或联合化疗临床研究的可靠性和完整性。因此，建议临床试验人员加强试验设计，确保试验设计、实施及报告的合理规范，同时SR/Meta分析也应同步提升质量，以期为临床科研工作者及决策者提供更可靠的循证医学证据。

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参考文献：

[1] Bray F,Ferlay J,Soerjomataram I,et al. Global cancer statistics 2018:GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin,2018,68(6):394-424.

[2] Ahmedin J,Freddin B,Melissa MC,et al. Global cancer statistics.[J]. CA Cancer J Clin,2011,61(2):69-90.

[3] Siegel RL,Miller KD,Jemal A. Cancer statistics,2018[J]. CA Cancer J Clin,2018,68(1):7-30.

[4] Lipson EJ,Forde PM,Hammers HJ,et al. Antagonists of PD-1 and PD-L1 in Cancer Treatment.[J]. Semin Oncol,2015,42(4):587-600.

[5] Gettinger S,Horn L,Jackman D,et al. Five-year follow-up of nivolumab in previously treated advanced non-small-cell lung cancer:results from the CA209-003 Study [J]. J Clin Oncol,2018,36(17):1675-1684.

[6] Landre T,Guetz GD,Chouahnia K,et al. First-line PD-1/PD-L1 inhibitor plus chemotherapy vs chemotherapy alone for negative or <1% PD-L1-expressing metastatic non-small-cell lung cancers [J]. J Cancer Res Clin Oncol,2020,146(2):441-448.

[7] Zhou GW,Xiong Y,Chen S,et al. Anti-PD-1/PD-L1 antibody therapy for pretreated advanced nonsmall-cell lung cancer:a meta-analysis of randomized clinical trials [J]. Medicine,2016,95(35):e4611.

[8] Moher D,Liberati A,Tetzlaff J,et al. Preferred reporting items for systematic reviews and meta-analyses:the PRISMA statement[J]. PLoS Med,2009,6(7):e1000097.

[9] Shea B,Reeves BC,Wells G,et al. AMSTAR 2:a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions,or both[J]. BMJ,2017,358:j4008.

[10] Atkins D,Best D,Briss PA,et al. Grading quality of evidence and strength of recommendations.[J]. BMJ,2004,328(7454):1490.

[11] Guyatt GH,Oxman AD,Vist G,et al. GRADE guidelines:4. Rating the quality of evidence—study limitations (risk of bias)[J]. J Clin Epidemiol,2011,64(4):407-415.

[12] Guyatt GH,Oxman AD,Kunz R,et al. GRADE guidelines 6. Rating the quality of evidence—imprecision [J]. J Clin Epidemiol,2011,64(12):1283-1293.

[13] Guyatt GH,Oxman AD,Kunz R,et al. GRADE guidelines:7. Rating the quality of evidence—inconsistency[J]. J Clin Epidemiol,2011,64(12):1294-1302.

[14] Guyatt GH,Oxman AD,Kunz R,et al. GRADE guidelines:8. Rating the quality of evidence—indirectness[J]. J Clin Epidemiol,2011,64(12):1303-1310.

[15] Guyatt GH,Oxman AD,Montori V,et al. GRADE guidelines:5. Rating the quality of evidence—publication bias [J]. J Clin Epidemiol,2011,64(12):1277-1282.

[16] Tartarone A,Roviello G,Lerose R,et al. Anti-PD-1 versus anti-PD-L1 therapy in patients with pretreated advanced non-small-cell lung cancer:a meta-analysis[J]. Future On-

col,2019,15(20):2423–2433.

[17] Khan M,Lin J,Liao G,et al. Comparative analysis of immune checkpoint inhibitors and chemotherapy in the treatment of advanced non-small cell lung cancer:a meta-analysis of randomized controlled trials[J]. Medicine (Baltimore),2018,97(33):e11936.

[18] Zhao Q,Xie R,Lin S,et al. Anti-PD-1/PD-L1 antibody therapy for pretreated advanced or metastatic nonsmall cell lung carcinomas and the correlation between PD-L1 expression and treatment effectiveness:an update Meta-analysis of randomized clinical trials [J]. BioMed Res Int,2018,2018:3820956.

[19] Zhou Y,Chen C,Zhang X,et al. Immune-checkpoint inhibitor plus chemotherapy versus conventional chemotherapy for first-line treatment in advanced non-small cell lung carcinoma:a systematic review and meta-analysis[J]. J Immunother Cancer,2018,6(1):155.

[20] Lee CK,Man J,Lord S,et al. Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced non-small cell lung carcinoma:a systematic review and Meta-analysis[J]. JAMA Oncol,2018,4(2):210–216.

[21] Jiang T,Liu H,Qiao M,et al. Impact of clinicopathologic features on the efficacy of PD-1/PD-L1 inhibitors in patients with previously treated non-small-cell lung cancer [J]. Clin Lung Cancer,2018,19(2):e177–e184.

[22] Pilotto S,Carbognin L,Rossi A,et al. Avoiding chemotherapy for advanced nononcogene addicted NSCLC overexpressing PD-L1:rule or option?[J]. Semin Oncol,2018,45(3):176–180.

[23] Peng TR,Tsai FP,Wu TW. Indirect comparison between pembrolizumab and nivolumab for the treatment of non-small cell lung cancer:a meta-analysis of randomized clinical trials[J]. Int Immunopharmacol,2017,49:85–94.

[24] Lee CK,Man J,Lord S,et al. Checkpoint inhibitors in metastatic EGFR-mutated non-small cell lung cancer—a Meta-analysis[J]. J Thorac Oncol,2017,12(2):403–407.

[25] 苏强,闫涵,侯艳丽,等. PD-1/PD-L1 抗体与多西他赛治疗晚期非小细胞肺癌安全性 Meta 分析 [J]. 中华肿瘤防治杂志,2016,23(21):1450–1454.
Su Q,Yan H,Hou YL,et al. Safety of PD-1/PD-L1 antibody versus docetaxel for advanced non-small cell lung cancer:a Meta analysis[J]. Chinese Journal of Cancer Prevention and Treatment,2016,23(21):1450–1454.

[26] 付鹏,王超,李翔,等. PD-1/PD-L1 抗体与多西紫杉醇治疗晚期非小细胞肺癌的总体疗效及安全性 Meta 分析 [J]. 肿瘤药学,2019,9(1):155–159.
Fu P,Wang C,Li X,et al. The overall efficacy and safety of PD-1/PD-L1 antibody and docetaxel in the treatment of advanced non-small cell lung cancer[J]. Anti-tumor Pharmacy,2019,9(1):155–159.

[27] 魏瑜,张莉. PD-1/PD-L1 抑制剂对比化疗一线治疗晚期非小细胞肺癌的 Meta 分析 [J]. 肿瘤防治研究,2019,46(5):440–446.
Wei Y,Zhang L. Efficacy and safety of PD-1/PD-L1 inhibitor versus chemotherapy in first-line treatment of advanced non-samll cell lung cancer:a Meta analysis [J]. Cancer Research on Prevention and Treatment,2019,46(5):440–446.

[28] 霍庚崴,宋莹,贾沙沙,等. PD-1/PD-L1 抑制剂联合化疗对比化疗一线治疗晚期非小细胞肺癌疗效及安全性的 Meta 分析[J]. 中国肿瘤生物治疗杂志,2020,27(3):309–314.
Huo GW,Song Y,Jia SS,et al. Comparison in treatment efficacy and safety between PD-1/PD-L1 inhibitor combined with chemotherapy alone as first-line treatment for advanced NSCLC:a Meta-analysis [J]. Chinese Journal of Cancer Biotherapy,2020,27(3):309–314.

[29] 姜爱民,程宇. PD-1/PD-L1 抑制剂治疗中晚期非小细胞肺癌疗效及安全性的 Meta 分析 [J]. 现代肿瘤医学,2020,28(20):3555–3560.
Jiang AM,Cheng Y. A Meta-analysis of efficacy and safety of PD-1/PD-L1 inhibitors for treatment of advanced non-small cell lung cancer [J]. Journal of Modern Oncology,2020,28(20):3555–3560.

[30] 宋鹏,尚聪聪,张力. PD-1/PD-L1 抑制剂治疗中青年和高龄非小细胞肺癌患者有效性的 Meta 分析 [J]. 山西医科大学学报,2018,49(11):1334–1340.
Song P,Shang CC,Zhang L. Efficacy of PD-1/PD-L1 inhibitors in the treatment of younger versus elderly non-small cell lung cancer patients:a Meta-analysis[J]. Journal of Shanxi Medical University,2018,49(11):1334–1340.

[31] 万秋,杨扬,黎友伦. PD-1 单抗/PD-L1 单抗与多西他赛治疗进展期非小细胞肺癌疗效与安全性的荟萃分析[J]. 中国新药杂志,2018,27(2):229–235.
Wan Q,Yang Y,Li YL. Efficacy and safety of PD-1 antibody/PD-L1 antibody versus docetaxel in non-small-cell lung cancer:a meta analysis [J]. Chinese Journal of New Drugs,2018,27(2):229–235.

[32] 张培培,丁大志,程纯. PD-1 单抗与含铂类化疗方案一线治疗晚期非小细胞肺癌疗效与安全性的 Meta 分析 [J]. 交通医学,2019,33(4):401–404.
Zhang PP,Ding DZ,Cheng C. Meta-analysis of the effica-

cy and safety of PD-1 monoclonal antibody and platinum-containing chemotherapy regimens for the first-line treatment of advanced non-small cell lung cancer [J]. Medical Journal of Communications,2019,33(4):401–404.

[33] 王丽亮,金津,杨洋,等. PD-1 抑制剂对晚期非小细胞肺癌治疗的有效性和安全性的 meta 分析 [J]. 重庆医学,2020,49(18):3107–3111.
Wang LL,Jin J,Yang Y,et al. Efficacy and safety of PD-1 inhibitors in the treatment of advanced non-small cell lung cancer:a meta analysis [J]. Chongqing Medicine,2020,49(18):3107–3111.

[34] 冯海明,赵晔,李敏,等. 抗 PD-1/PD-L1 单抗治疗晚期非小细胞肺癌有效性和安全性的单组率的 Meta 分析[J]. 中国循证医学杂志,2018,18(3):322–333.
Feng HM,Zhao Y,Li M,et al. Efficacy and safety of anti PD-1/PD-L1 in the treatment of advanced non-small-lung cancer:a single arm meta-analysis [J]. Chinese Journal of Evidence-Based Medicine,2018,18(3):322–333.

[35] 王心怡, 李晨露. 抗 PD-L1 药物治疗进展期难治型 NSCLC 有效性与安全性 Meta 分析[J]. 青岛大学医学院学报,2016,52(6):659–664.
Wang XY,Li CL. Anti-PD-L1 antibody for non-small cell lung cancer:a Meta analysis of effectiveness and safety[J]. Journal of Qingdao University(Medical Sciences),2016,52(6):659–664.

[36] 周俊翔,蒋刚,蔡红. 抗程序性死亡因子及其配体单抗治疗晚期非小细胞肺癌 Meta 分析 [J]. 中国药业,2018,27(19):45–49.
Zhou JX,Jiang G,Cai H. Effect of Anti-PD-1/PD-L1 antibodies in the treatment of advanced non-small-cell lung cancer:a Meta-analysis [J]. China Pharmaceuticals,2018,27(19):45–49.

[37] 陈丽君,赵鹏,曹科,等. 免疫检查点抑制剂治疗非小细胞肺癌患者有效性及安全性的 Meta 分析 [J]. 肿瘤,2018,38(8):780–791.
Chen LJ,Zhao P,Cao K,et al. Efficacy and safety of immune checkpoint inhibitors in the treatment of non-small cell lung cancer:a meta-analysis [J]. Tumor,2018,38(8):780–791.

[38] 丁芸兰,周海辉,周玉皆. 免疫卡控点抑制剂联合化疗一线治疗晚期非小细胞肺癌的疗效与安全性 Meta 分析 [J]. 药物流行病学杂志,2019,28(8):498–506.
Ding YL,Zhou HH,Zhou YJ. Efficacy and safety of immune checkpoint inhibitors plus chemotherapy as a first-line treatment for advanced non-small-cell lung cancer:a Meta-analysis[J]. Chinese Journal of Pharmacoepidemiology,2019,28(8):498–506.

[39] Pussegoda K,Turner L,Garritty C,et al. Systematic review adherence to methodological or reporting quality [J]. Syst Rev,2017,6(1):1–14.

[40] Schünemann HJ,Fretheim A,Oxman AD. Improving the use of research evidence in guideline development:1. Guidelines for guidelines [J]. Health Res Policy Syst,2006,4(1):13.

[41] Rittmeyer A,Barlesi F,Waterkamp D,et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK):a phase 3,open-label,multicentre randomised controlled trial [J]. Lancet,2017,389(10066):255–265.

[42] Hui R,Garon EB,Goldman JW,et al. Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer:a phase 1 trial[J]. Ann Oncol,2017,28(4):874–881.

[43] Kottke T,Evgin L,Shim KG,et al. Subversion of NK-cell and TNFalpha immune surveillance drives tumor recurrence[J]. Cancer Immunol Res,2017,5(11):1029–1045.