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关于PD-1/PD-L1免疫抑制剂治疗晚期食管癌疗效和安全性的Meta分析

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摘　要

目的：系统评价PD-1/PD-L1免疫抑制剂应用于晚期食管癌的疗效和安全性。方法：检索PubMed、EMbase、Web of Science、The Cochrane Library、Clinical Trials等数据库搜寻关于PD-1/PD-L1免疫抑制剂治疗晚期食管癌的随机对照研究，并由两名独立人员筛选文献和提取相关数据。检索时限为2016年1月~2021年12月，并对纳入的研究文献进行评价，应用RevMan 5.3软件进行分析OR及其对应的95%置信区间。结果：按照纳入和排除标准，保留5项随机对照研究，包括1685例患者。Meta分析结果显示，免疫治疗组12个月总生存期(OS)发生率(OR = 1.95, 95% CI: 1.51~2.51, *P* < 0.00001)、18个月OS发生率(OR = 1.80, 95% CI: 1.28~2.52, *P* = 0.0007)和12个月无进展生存期(PFS)发生率(OR = 1.77, 95% CI: 1.15~2.72, *P* = 0.009)、18个月PFS发生率(OR = 2.10, 95% CI: 1.09~4.04, *P* = 0.03)均高于对照组，差异有统计学意义。针对PD-L1表达阳性(联合阳性评分CPS > 10)的亚组人群中，免疫治疗可明显提高12个月OS发生率(OR = 2.91, 95% CI: 1.56~5.41, *P* = 0.0008)。对于安全性方面，免疫治疗组总体不良发生率(OR = 0.26, 95% CI: 0.08~0.85, *P* = 0.03)，3~5级不良反应发生率(OR = 0.29, 95% CI: 0.12~0.75, *P* = 0.01)均小于对照组，且差异有统计学意义。结论：对于晚期食管癌患者，抗PD-1/PD-L1免疫治疗的疗效优于化疗或姑息治疗，且安全性高。

关键词

晚期食管癌，PD-1/PD-L1免疫抑制剂，免疫治疗，生存期，安全性

The Efficacy and Safety of PD-1/PD-L1 Immunosuppressive Agents in Advanced Esophageal Cancer: A Meta-Analysis

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Abstract

Objective: To systematically evaluate the efficacy and safety of PD-1/PD-L1 immunosuppressive agents in advanced esophageal cancer. Method: The databases PubMed, EMBASE, web of science, the Cochrane Library, clinical trials were searched for randomized controlled studies on PD-1/PD-L1 immunosuppressive therapy for advanced esophageal cancer, and two independent personnel screened the literature and extracted relevant data. The search time frame was from January 2016 to December 2021, and the literature of included studies was evaluated and RevMan 5.3 software was used to analyze OR and their corresponding 95% confidence intervals. Result: Following the inclusion and exclusion criteria, 5 RCTs including 1685 patients were retained. Meta analysis showed that the incidence of 12-month overall survival (OS) (OR = 1.95, 95% CI: 1.51~2.51, *P* < 0.00001), 18-month OS (OR = 1.80, 95% CI: 1.28~2.52, *P* = 0.0007) and 12-month progression free survival (PFS) (OR = 1.77, 95% CI: 1.15~2.72, *P* = 0.009) were higher in the immunotherapy group than in the control group, with significant differences. In the subgroup of patients with positive PD-L1 expression (combined positive score CPS > 10), immunotherapy significantly improved the 12-month OS rate (OR = 2.91, 95% CI: 1.56~5.41, *P* = 0.0008). In terms of safety, the overall incidence of adverse reactions (OR = 0.26, 95% CI: 0.08~0.85, *P* = 0.03) and the incidence of grade 3~5 adverse reactions (OR = 0.29, 95% CI: 0.12~0.75, *P* = 0.01) in the immunotherapy group were lower than those in the control group, and the difference was statistically significant. Conclusion: For patients with advanced esophageal cancer, the efficacy of anti-PD-1/PD-L1 immunotherapy is superior to that of chemotherapy or palliative therapy, and the safety profile is high.

Keywords

Advanced Esophageal Cancer, PD-1/PD-L1 Immunosuppressive Agents, Immunotherapy, Survival, Security

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1. 引言

食管癌是世界上第七大常见恶性肿瘤，且发病率呈逐年上升趋势[1]。早期食管癌的临床症状不明显，约 40%的患者确诊时已经是局部晚期或已有远处转移[2]，意味着没有机会进行根治性手术。由于晚期食管失去了手术治疗的机会，主要采用放化疗或靶向治疗[3] [4] [5]。然而，化疗和靶向治疗的效果有限，复发率和转移率很高，5 年生存率只有 15%~25% [6]。基于上述治疗情况，为了提高生存率，减少局部和远处复发，新辅助治疗已经开始使用。

免疫治疗开启了食管癌治疗的新篇章。由于肿瘤细胞抗原表达的缺乏或免疫耐受环境的建立，使恶性肿瘤具有逃避免疫监视的特点。尽管胃肠道恶性肿瘤并不是传统的免疫原性恶性肿瘤，但一些研究证实了肿瘤周围浸润淋巴细胞的数量与肿瘤进展和预后密切相关[7] [8] [9]。近年来，以程序性死亡受体 1/程序性死亡配体 1 (Programmed cell death-1/Programmed cell death-ligand 1, PD-1/PD-L1)信号通路研发的 PD-1/PD-L1 抑制剂成为热点，已用于黑色素瘤、非小细胞肺癌(Non small cell lung cancer, NSCLC)和消化

系统肿瘤的治疗[10] [11] [12]。与传统治疗相比，PD-1/PD-L1 抑制剂带来的持续治疗反应非常可观，是胃肠道恶性肿瘤治疗上的一个新方向。在这项 Meta 分析中，我们试图全面分析抗 PD-1/PD-L1 免疫治疗在晚期食管癌中的疗效和安全性，从而为晚期食管癌的免疫治疗提供可能依据，更好地指导临床。

2. 资料与方法

2.1. 文献检索

计算机检索 PubMed、EMbase、Web of Science、The Cochrane Library、Clinical Trials 等数据库，搜查有关 PD-1/PD-L1 抑制剂免疫治疗晚期食管癌的相关随机对照试验(Randomized controlled trials, RCT)报道，检索时限为 2016 年 1 月~2021 年 12 月。检索策略采用主题词结合关键词的方式，辅以手动检索纳入搜索文献中的参考文献。英文检索词包括 advanced esophageal cancer、esophageal cancer、advanced esophageal carcinoma、esophageal、Immune checkpoint inhibitors、PD-1 inhibitors、PD-L1 inhibitors 和 immunotherapy。

2.2. 纳入、排除标准

2.2.1. 纳入标准

1) 随机临床试验；2) 转移性或晚期食管癌；3) 一线治疗后；4) 可获得总生存期(overall survival, OS)，无进展生存期(progression free survival, PFS)，客观缓解率(objective response rate, ORR)和不良反应等可用数据的文献。

2.2.2. 排除标准

1) 重复报告的文献；2) 非 RCTs；3) 用于一线治疗或围手术期治疗的文章；4) 免疫治疗与其它治疗方案相结合、缺乏生存数据或不良反应的文章；5) 书籍、病例报告、动物试验等相关文献及非英文文章。

2.3. 结局指标

包括疗效指标和安全性指标。疗效指标包括 ORR 和 6 个月、12 个月和 18 个月 OS 及 PFS 的发生率；安全性指标指免疫治疗相关毒副反应发生率等。

2.4. 资料提取

由 2 名独立的研究人员按统一流程和表格进行文献筛选和提取资料并复核，如有分歧求助第三研究人员。资料提取内容包括：研究题目、第一作者、发表时间及杂志；研究样本量、性别、年龄等基本资料；对照组具体方案；质量评价指标及结局指标数据。

2.5. 文献质量评价

采用 Cochrane 手册 5.10 针对 RCTs 的偏倚风险评估工具来评价纳入研究的偏倚风险。并应用改良的 Jadad 量表[13]评估所纳入研究的质量，内容包括随机化、随机序列的生成、盲法、退出和失访。文献评价由两位作者独立评分。一般认为 1~3 分为低质量，4~7 分为高质量。

2.6. 统计学分析

采用 RevMan5.3 软件进行 Meta 分析。研究中，所有的分类变量都是不连续的。对于异质性评估，我们使用 I^2 来评估纳入的研究。如果 I^2 低于 50%，则认为统计分析没有显著的异质性，使用固定效应模型(Fixed effect model, FEM)；如果 I^2 高于或等于 50%，则认为统计分析存在异质性，使用随机效应模型(Random effect model, REM)。比值比(Odds ratio, OR)，95%置信区间(Confidence intervals, CI)和 P 值用于评估各效应指标的结果差异，$P < 0.05$ 时认为差异具有统计学意义。

3. 结果

3.1. 文献筛选结果

在线数据库检索出 243 项研究。经过粗略筛选，52 篇重复文章被排除在外，157 篇因题目或摘要不符合要求及非随机对照实验。阅读全文后，按照纳入和排除标准，最终纳入 5 项 RCTs，共计食管癌患者 1685 例[14] [15] [16] [17] [18]。

3.2. 纳入研究的基本特征和质量评价

所有纳入的临床试验均为随机、前瞻性和多中心设计(表 1)。所纳入的研究对随机分配方案的产生、分配隐藏描述完整。所有纳入研究不存在退出和失访情况。1 篇所纳入研究的为开放性(图 1)。应用改良的 Jadad 量表用于评估所纳入研究的质量，有 4 项临床研究 Jadad 评分达到 6~7 分，另外一项临床研究达到 5 分(表 2)。

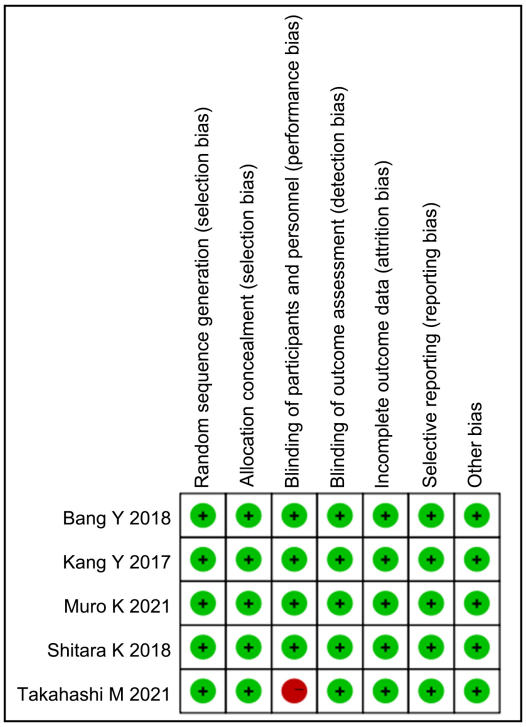

Figure 1. Summary of risk of bias in included studies
图 1. 纳入研究风险偏倚总结

Table 1. Basic characteristics of the included literature research
表 1. 所纳入文献研究的基本特征

随访项目	研究类型	患者数量(例)	实验组干预措施	对照组干预措施
Muro K 2021	前瞻性、多中心随机对照实验	152 例	Pembrolizumab (77 例)	化疗(75 例)
Shitara K 2018	前瞻性、多中心随机对照实验	395 例	Pembrolizumab (196 例)	化疗(199 例)
Bang Y 2018	前瞻性、多中心随机对照实验	371 例	Avelumab (185 例)	化疗(186 例)
Kang Y 2017	前瞻性、多中心随机对照实验	493 例	Nivolumab (330 例)	安慰剂(163 例)
Takahashi M 2021	前瞻性、多中心随机对照实验	274 例	Nivolumab (136 例)	化疗(138 例)

Table 2. Jadad scale
表 2. Jadad 量表

评价指标	Muro K 2021	Shitara K 2018	Bang Y 2018	Kang Y 2017	Takahashi M 2021
随机序列的产生	1	2	1	2	2
随机化隐藏	2	2	2	2	2
盲法	2	2	2	2	2
退出与失访	0	1	1	1	0
得分	5	7	6	7	6

Note: The total score is 7 points, with 1~3 points considered low quality and 4~7 points considered high quality.
注：总分为 7 分，1~3 分视为低质量，4~7 分视为高质量。

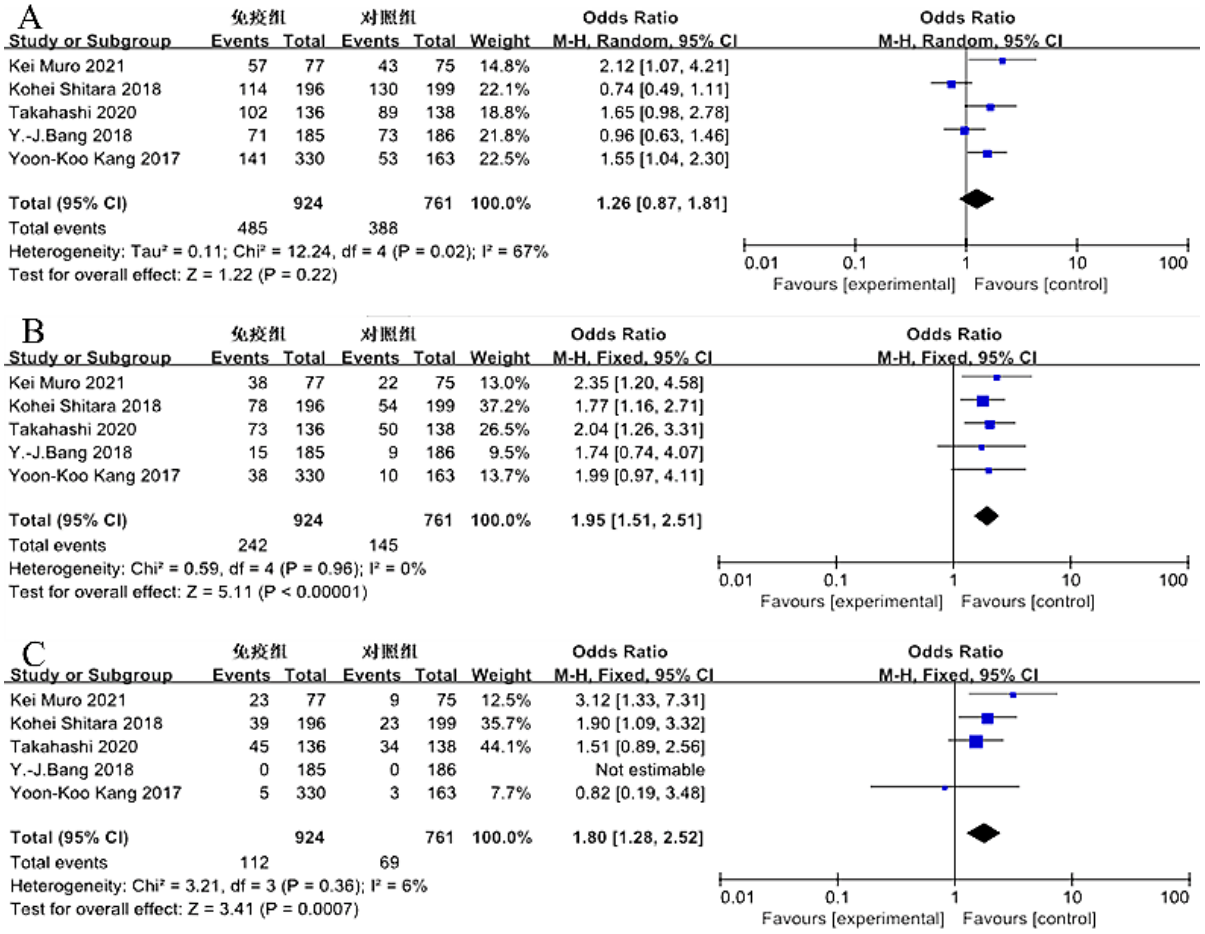

Figure 2. Immunotherapy group and control group overall survival (OS) Meta analysis. (A) 6-month OS analysis; (B) 12-month OS analysis; (C) 18-month OS analysis
图 2. 免疫治疗组和对照组总生存期(OS) Meta 分析。(A) 6 个月 OS 分析；(B) 12 个月 OS 分析；(C) 18 个月 OS 分析

3.3. Meta 分析结果

3.3.1. 长期生存情况

Meta 分析纳入研究患者 6 个月、12 个月和 18 个月的 OS 和 PFS 发生率。在 6 个月的 OS 发生率方面，免疫治疗组与对照组无显著差异(图 2(A)) (OR = 1.26, 95% CI: 0.87~1.81, *P* = 0.22)。而 12 个月 OS (OR

= 1.95, 95% CI: 1.51~2.51, P < 0.00001) (图 2(B))和 18 个月 OS 发生率(OR = 1.80, 95% CI: 1.28~2.52, P = 0.0007) (图 2(C))差异明显，具有统计学意义。对 PFS 数据的分析显示，免疫治疗组和对照组之间的 6 个月 PFS 发生率(OR = 1.16, 95% CI: 0.63~2.15, P = 0.63) (图 3(A))没有显著差异，而 12 个月 PFS 发生率(OR = 1.77, 95% CI: 1.15~2.72, P = 0.009) (图 3(B))及 18 个月 PFS 发生率(OR = 2.10, 95% CI: 1.19~4.04, P = 0.03) (图 3(C))差异明显，具有统计学意义。

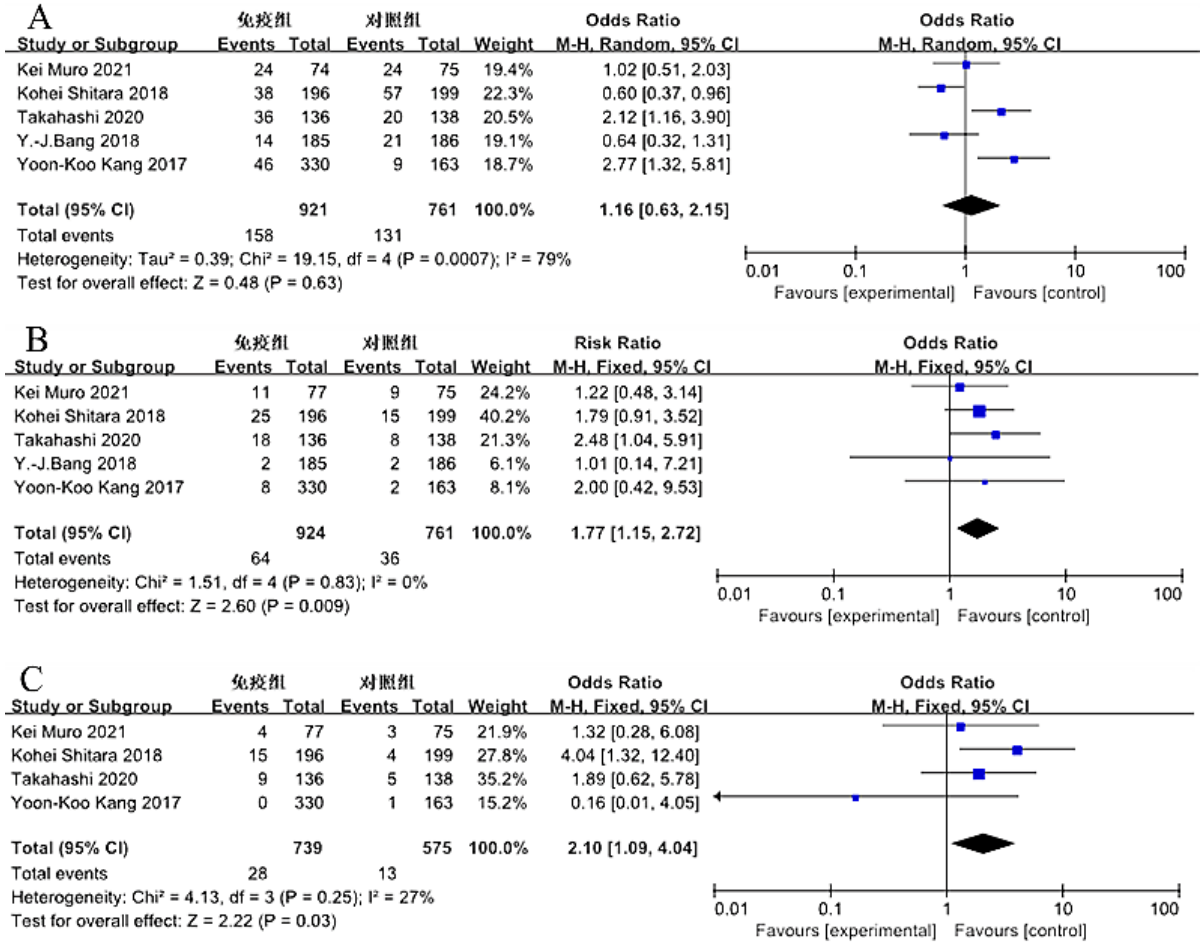

Figure 3. Meta analysis of progression free survival (PFS) in immunotherapy group and control group. (A) 6-months PFS; (B) 12-months PFS; (C) 18-months PFS
图 3. 免疫治疗组和对照组无进展生存期(PFS) Meta 分析。(A) 6 个月 PFS；(B) 12 个月 PFS；(C) 18 个月 PFS

3.3.2. 客观缓解率和亚组分析

ORR 指肿瘤缩小达到一定量并且保持一定时间的病人的比例，包括完全缓解(Complete remission, CR)和部分缓解(Partial remission, PR)的病例。其中纳入的 4 项研究都记录了 ORR 的数据。ORR 的 Meta 分析如图 4(A)所示。结果显示，免疫治疗组与对照组的 ORR 无显著差异(OR = 1.54, 95% CI: 0.52~4.55, P = 0.43)。此外，我们评估了联合阳性分数(Combined Positive Score, CPS) ≥ 10 的亚组人群(图 4(B))。纳入的研究只有 Muro K 和 ShitaraK 二人报告了相关数据。Meta 分析显示，在 PD-L1 CPS ≥ 10 的亚组人群中，免疫治疗组和对照组 12 个月 OS 发生率差异明显(OR = 2.91, 95% CI: 1.56~5.41, P = 0.0008)，免疫治疗占优势。不足的是缺乏 CPS < 1 的亚组患者相关数据。

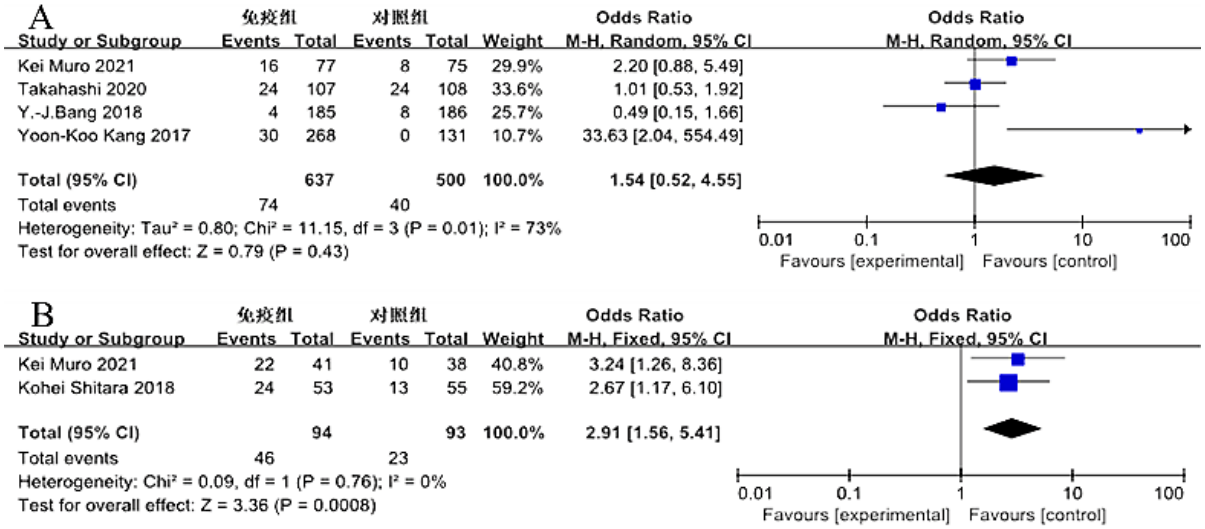

Figure 4. Meta analysis of ORR (A) and 12-month OS (B) in patients with CPS > 10 subgroups by PD-L1 expression in immunotherapy and control arms
图 4. 免疫治疗组和对照组 ORR (A)和 PD-L1 表达 CPS > 10 亚组患者 12 个月 OS (B)的 Meta 分析

3.3.3. 安全性分析

参考世界卫生组织(World Health Organization, WHO)抗癌药物常见毒副反应分级标准(0~IV 级)对 5 项临床研究的治疗相关毒副反应进行了分析，将III级及 III 级以上的毒副反应定义为重度。结果显示，免疫治疗组和对照组总体毒副反应的发生率(OR = 0.26, 95% CI: 0.08~0.85, P = 0.03)及重度治疗相关毒副反应的发生率(OR = 0.29, 95% CI: 0.12~0.75, P = 0.01)，二组间比较差异具有统计学意义，提示免疫治疗相关毒副反应相对较小，安全性高(图 5)。

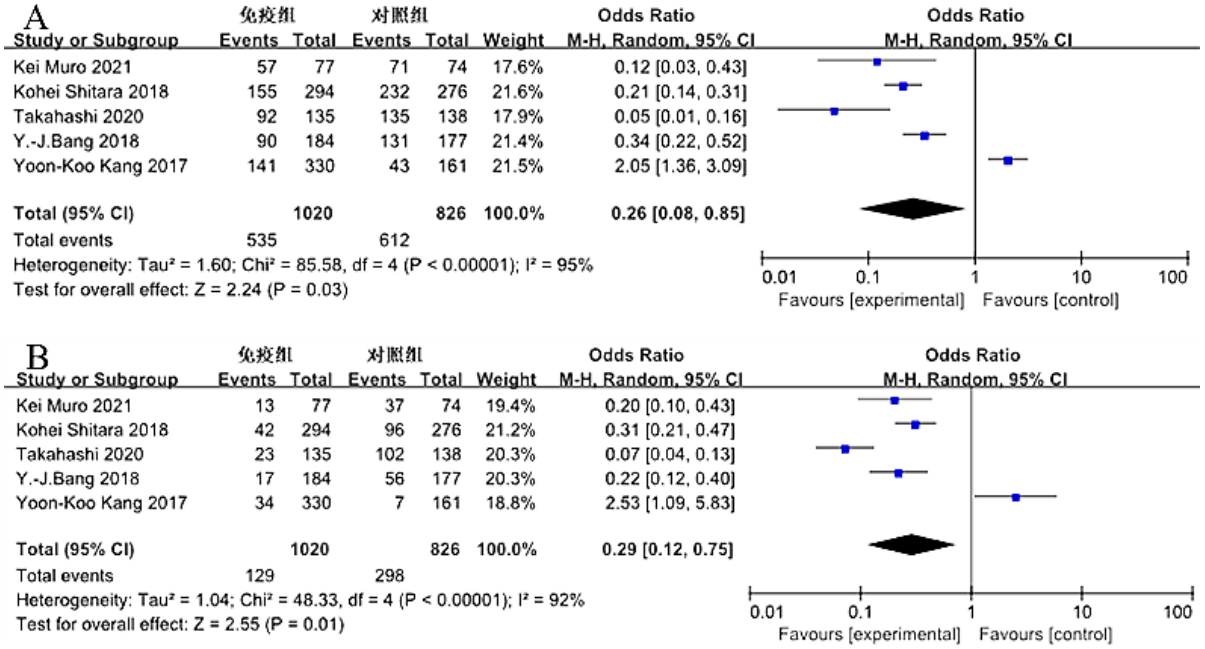

Figure 5. Meta analysis representing the incidence of overall toxicities (A) and severe toxicities (B) in the two groups of patients, respectively
图 5. 分别表示二组患者总体毒副反应(A)和重度毒副反应(B)发生率的 Meta 分析

4. 讨论

食管癌是我国常见的消化道恶性肿瘤，仅仅约 20%患者在确诊时可行根治性手术治疗，且 5 年生存率仅为 20%左右[19]；另外约 80%患者在确诊时已属中晚期，已无法进行手术治疗，治疗上只能局限在放疗和化疗，其预后效果并不满意，局部肿瘤不易控制、复发率高[20]。人们逐渐认识到肿瘤免疫微环境(Tumor immune microenvironment, TIME)在恶性肿瘤中的生物学作用和意义，免疫检查点信号通路成为目前晚期食管癌免疫治疗领域的热点。

免疫检查点信号通路主要由细胞毒性 T 淋巴细胞相关抗原 4 (Cytotoxic T-lymphocyte-associated antigen 4, CTLA-4)通路和 PD-1/PD-L1 通路组成[21]。PD-1 是一种主要表达于活化 T 细胞上的负性共刺激受体，它与配体 PD-L1 和 PD-L2 结合后可下调 T 细胞介导的免疫反应，从而抑制 T 淋巴细胞和肿瘤浸润淋巴细胞(Tumor infiltrating lymphocyte, TIL)的功能[22] [23] [24]。多种类型的肿瘤细胞可通过增加或激活 PD-L1 的表达达到免疫逃逸的目的[25] [26]，而免疫治疗的目的就是通过增强免疫系统对癌细胞的靶向性和破坏性来增强机体的自然免疫反应[27]。

目前，针对 PD-1/PD-L1 通路的多种靶向药物已成功进入临床试验[28]，包括信迪利单抗和纳武利尤单抗在内的一些药物已经被 FDA 批准上市。在消化道恶性肿瘤领域，目前正在进行并已经完成多项临床研究，并获得满意临床疗效[29] [30]。本研究运用 Meta 分析评估了 PD-1/PD-L1 通路的相关免疫药物在晚期食管癌中的疗效和安全性。我们在回顾性随机对照试验的基础上，通过分析 OS、PFS、ORR 等指标及亚组分析发现抗 PD-1/PD-L1 免疫治疗可以带来长期生存的益处，对指导免疫药物在食管癌中的应用有一定的指导价值。

我们的研究还分析了免疫治疗组和对照组之间的不良反应。在不良反应方面，免疫治疗具有明显的安全性优势。总体毒副反应的发生率及严重不良反应发生率(III 级以上)方面，免疫治疗组的发病率均显著低于对照组。临床上使用的抗肿瘤化疗药物具有不同程度的毒副作用，一些严重的毒副作用与药物的剂量和使用直接相关，如血细胞减少(白细胞、血小板、血红蛋白、粒细胞等)、胃肠道反应(恶心、呕吐、腹泻、便秘)、肝功能异常、肾功能异常、心脏毒性、神经功能异常等[31] [32]。与传统化疗相比，免疫治疗的毒副作用(免疫相关不良事件)通常较少。免疫相关不良事件通常分为 1~2 级，通常在患者可以耐受的范围内，大多不需要特殊处理，即使需要治疗，也可以通过简单的对症治疗迅速恢复。更重要的是，这些副作用并不影响疗效。

此外，本次研究尚存在一些不足：① 影响疗效因素，如患者年龄、免疫治疗频次及周期等未纳入分析；② 肿瘤突变负荷(Tumor Mutation Burden, TMB)、微卫星不稳定性(Microsatellite Instability, MSI)和 T 细胞受体(T cell receptor, TCR)等相关数据无法从所纳入的文献中提取，无法进行深入分析；③ 可能存在选择性偏倚；④ 本研究中包含的随机对照试验较少等。我们期待更深入的分层分析，寻找出更有说服力的研究证据以确定免疫治疗的受益群体、疗效和安全性。

5. 总结

综上所述，对于晚期食管癌的治疗，抗 PD-1/PD-L1 免疫疗法的治疗效果优于化疗或姑息治疗，长期生存率显著较高。此外，此次分析研究显示 PD-L1 表达 CPS ≥ 10 亚组患者似乎比总人群受益更显著。免疫治疗组的副作用发生率较低，且安全性可控。抗 PD-1/PD-L1 免疫治疗是晚期食管癌患者二线或后期治疗的新选择。

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