直接抗病毒药物治疗丙型肝炎病毒后肝细胞癌的发生或复发：系统评价和 Meta 分析

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【摘要】背景与目的 直接抗病毒药物（direct-acting antivirals, DAAs）治疗丙型肝炎病毒（hepatitis C virus, HCV）后，肝细胞癌（hepatocellular carcinoma, HCC）的发生或复发风险存在争议。本研究通过 Meta 分析评估接受直接抗病毒药物治疗患者的肝细胞癌发生或复发特征。**方法** 检索截至 2024 年 12 月 31 日发表在 PubMed、Embase 和 Web of Science 数据库中的相关文献，采用随机效应模型 Meta 分析计算肝细胞癌的发生或复发率的综合估计值。**结果** 共纳入 78 项研究（140614 例患者），其中 50 项研究涉及肝细胞癌发生（136689 例患者，前瞻性 19 项、回顾性 29 项、回顾-前瞻性 1 项、观察性 1 项），42 项研究涉及肝细胞癌复发（3925 例患者，前瞻性 14 项、回顾性 25 项、回顾-前瞻性 2 项、观察性 1 项）。在肝细胞癌发生的研究中，合并肝细胞癌发生率为 3%（95%置信区间 3%-4%）；在肝细胞癌复发的研究中，合并肝细胞癌复发率为 32%（95%置信区间 26%-38%）。多变量方差分析显示，接受直接抗病毒药物治疗的患者与接受干扰素治疗或未治疗的患者相比，肝细胞癌的发生或复发率相近甚至更低。**结论** 现有数据表明，直接抗病毒药物治疗后肝细胞癌的发生或复发率处于可接受范围。与接受干扰素治疗或未治疗的患者相比，直接抗病毒药物治疗与肝细胞癌发生或复发的风险相近。我们建议对晚期肝病和肝细胞癌高风险患者加强病毒清除后的监测。

【关键词】直接抗病毒药物；肝细胞癌；丙型肝炎病毒；发生；复发
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The occurrence or recurrence of hepatocellular carcinoma after hepatitis c virus therapy with direct-acting antivirals: systematic reviews and Meta-analyses

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【Abstract】Background and Aims The risk of hepatocellular carcinoma (HCC) occurrence or recurrence after treatment of hepatitis C virus (HCV) with direct-acting antivirals (DAAs) remains controversial. We performed a meta-analysis to evaluate the occurrence or recurrence characteristics of HCC in DAAs-treated patients. **Methods** A search was conducted for reports published in PubMed, Embase and Web of Science up to December 31, 2024. Random-effects meta-analyses were performed to determine composite estimates of HCC incidence or recurrence rate. **Results** A total of 78 studies (n = 140614 patients), including 50 studies on HCC occurrence (n = 136689 patients, prospective = 19, retrospective = 29, retrospective-prospective = 1, observational = 1), and 42 studies on HCC recurrence (n=3925 patients prospective=14,

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retrospective=25 and retrospective-prospective=2, observational=1). In the studies with HCC occurrence, the combined HCC incidence was 3% (95%CI 3-4%), and in the studies with HCC recurrence, the combined HCC recurrence rate was 32% (95%CI 26-38%). In multivariate analysis of variance, HCC incidence or recurrence rates were similar or even lower in patients treated with DAAs than in patients treated with IFN or untreated. **Conclusions** Current data suggest an acceptable rate of HCC incidence or recurrence after DAAs therapy. DAAs treatment was associated with a similar risk of HCC occurrence or recurrence compared with interferon-treated or untreated patients. We recommend enhanced implementation of post-eradication surveillance of viral infection in patients with advanced liver disease and higher risk of HCC.

【Keywords】Direct-acting antivirals; Hepatocellular carcinoma; Hepatitis C virus; Occurrence; Recurrence

1 引言

根据 2020 年的统计数据，肝癌是全球第六大常见癌症，也是第三大癌症死亡原因[1]。其中，慢性丙型肝炎（hepatitis C virus, HCV）是西方国家（欧美地区）原发性肝细胞癌最常见的病因。尽管肝移植、切除和射频消融术延长了肝癌患者的生存时间[2]，但其 5 年复发率仍高达 50%[3]。预测显示，到 2040 年，肝癌的新增病例数和死亡数可能增加 55%以上[4]。

直接抗病毒药物（DAAs）已成为丙型肝炎病毒的标准治疗方案，病毒清除率超过 90%[5]。研究表明，直接抗病毒药物治疗可改善肝纤维化和门静脉高压[6]。然而，有研究显示接受直接抗病毒药物治疗的患者肝细胞癌的发生和复发风险增加[7]，这引发了关于直接抗病毒药物的安全性及其与肝细胞癌发生相关性的争议。尽管先前的系统评价和 Meta 分析表明，直接抗病毒药物治疗并未显著增加肝细胞癌的复发率[8,9]，但纳入的研究数量有限。近年来，来自不同中心和国家的新研究为这一主题提供了更多证据。

因此，本系统评价和 Meta 分析的主要目的是：评估无既往肝细胞癌病史的慢性丙型肝炎患者接受直接抗病毒药物治疗后肝细胞癌的发生率；评估接受肝细胞癌根治性治疗的慢性丙型肝炎患者接受直接抗病毒药物治疗后肝细胞癌的复发率。次要目的是：比较无既往肝细胞癌病史的慢性丙型肝炎患者接受直接抗病毒药物治疗与干扰素治疗或未治疗后肝细胞癌的发生风险；比较接受肝细胞癌根治性治疗的慢性丙型肝炎患者接受直接抗病毒药物治疗与干扰素治疗或未治疗后肝细胞癌的复发风险。

2 方法

2.1 信息来源与检索策略

我们检索了截至 2024 年 12 月 31 日 PubMed、Embase 和 Web of Science 数据库，使用的医学主题词（Medical Subject Headings, MeSH）和关键词包括“直接抗病毒药物”“丙型肝炎病毒”和“肝细胞癌”。PubMed 的检索式为（（“hepatitis c, chronic”[MeSH Terms] OR “hepacivirus”[MeSH Terms]））AND（（“liver neoplasms”[MeSH Terms] OR “carcinoma，hepatocellular”[MeSH Terms] OR “liver neoplasms”[MeSH Terms]））AND（（direct-acting antivirals）OR（interferon-free）OR（DAAs））。本研究遵循系统评价和 Meta 分析优先报告条目（PRISMA）声明进行（PRISMA checklist 作为补充信息表 S3）。我们采用纽卡斯尔-渥太华量表的修订版评估纳入研究的质量[10]，该量表将纳入研究的偏倚风险分为四个等级（即未知、低、中、高）。本研究已在 PROSPERO 数据库注册（编号：CRD42023449487）。

表 S3　系统评价与 Meta 分析优先报告条目（PRISMA）清单

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review.	Page 1
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2, 3
		INTRODUCTION	Page 3, 4
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
		METHODS	Page 4,5
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	

Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 5
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1,2; Page5, 6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S1, S2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Fig.2,3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Fig.2,3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 6, 7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 6, 7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 6, 7

Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 6, 7
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 6, 7
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 7-9
	23b	Discuss any limitations of the evidence included in the review.	Page 7-9
	23c	Discuss any limitations of the review processes used.	Page 7-9
	23d	Discuss implications of the results for practice, policy, and future research.	Page 7-9
		OTHER INFORMATION	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	CRD42023449487
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 8
Competing interests	26	Declare any competing interests of review authors.	Page 8
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 8

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.For more information, visit: http://www.prisma-statement.org/

2.2 研究选择与纳入标准

纳入系统评价的研究需报告接受直接抗病毒药物治疗患者的肝细胞癌发生或复发情况。纳入标准：（1）使用任何直接抗病毒药物单药或联合治疗的慢性丙型肝炎患者；（2）评估直接抗病毒药物治疗后肝细胞癌的发生或复发情况，并报告直接抗病毒药物治疗后发生或复发的患者比例；（3）前瞻性和回顾性研究。排除标准：（1）非人类研究；（2）无法提取原始数据的研究；（3）非英文文献。首先筛选标题和摘要，然后评估符合纳入标准的文章全文并提取数据。作者随后评估符合纳入标准的文章全文，任何不确定的问题通过与其他评审员讨论解决。

2.3 数据收集过程

由杨豪洁独立评估文章是否符合纳入标准，并由独立评审员王钰鲲验证。为每项研究提取以下信息：研究设计、国家、研究类型、接受直接抗病毒药物治疗的人数、性别、平均年龄、持续病毒学应答率、肝细胞癌的发生或复发情况、平均随访时间等。

2.4 统计分析

使用 STATA 16.0 软件（StataCorp LP，美国）进行统计分析。根据纳入研究的异质性，考虑两种模型：固定效应模型（Mantel-Haenszel）和随机效应模型（Der Simonian 和 Laird）的 Meta 分析。在合并数据之前，我们评估了所有研究的异质性。采用 Cochran's Q 统计量评估研究间的异质性，采用 I^2统计量评估不一致性，该统计量衡量研究间因异质性而非偶然因素导致的总变异百分比。I^2值为 0%表示无观察到的异质性，而 0%-100%的值表示异质性逐渐增加。当 I^2值<50%（P 值>0.1）时，采用固定效应模型估计合并效应量；当同质性假设无效（P 值<0.1）且 I^2>50%时，采用随机效应模型[11]。通过根据研究设计、研究地点和中位随访时间进行亚组 Meta 分析模型，探讨异质性的潜在来源。在可能的情况下，进行比例 Meta 分析以确定发生和复发率，并以合并比例报告。对于有对照组的研究，我们将酌情使用风险比或比值比进行 Meta 分析。采用 Egger 检验评估发表偏倚[12]。

3 结果

3.1 研究特征

最初，通过数据库检索共确定 3778 篇引文，其中 76 篇最终进行全文审查。78 项独特的研究[7,13-87]（140614 例患者）被纳入定量合成和 Meta 分析，包括 50 项关于肝细胞癌发生的研究（136689 例患者）和 42 项关于肝细胞癌复发的研究（3925 例患者）。在肝细胞癌发生的研究中，19 项为前瞻性研究，29 项为回顾性研究，1 项为回顾-前瞻性研究，1 项为观察性研究，33 项为多中心研究；在肝细胞癌复发的研究中，14 项为前瞻性研究，25 项为回顾性研究，2 项为回顾-前瞻性研究，1 项为观察性研究，26 项为多中心研究。研究特征详见表 1 和表 2。

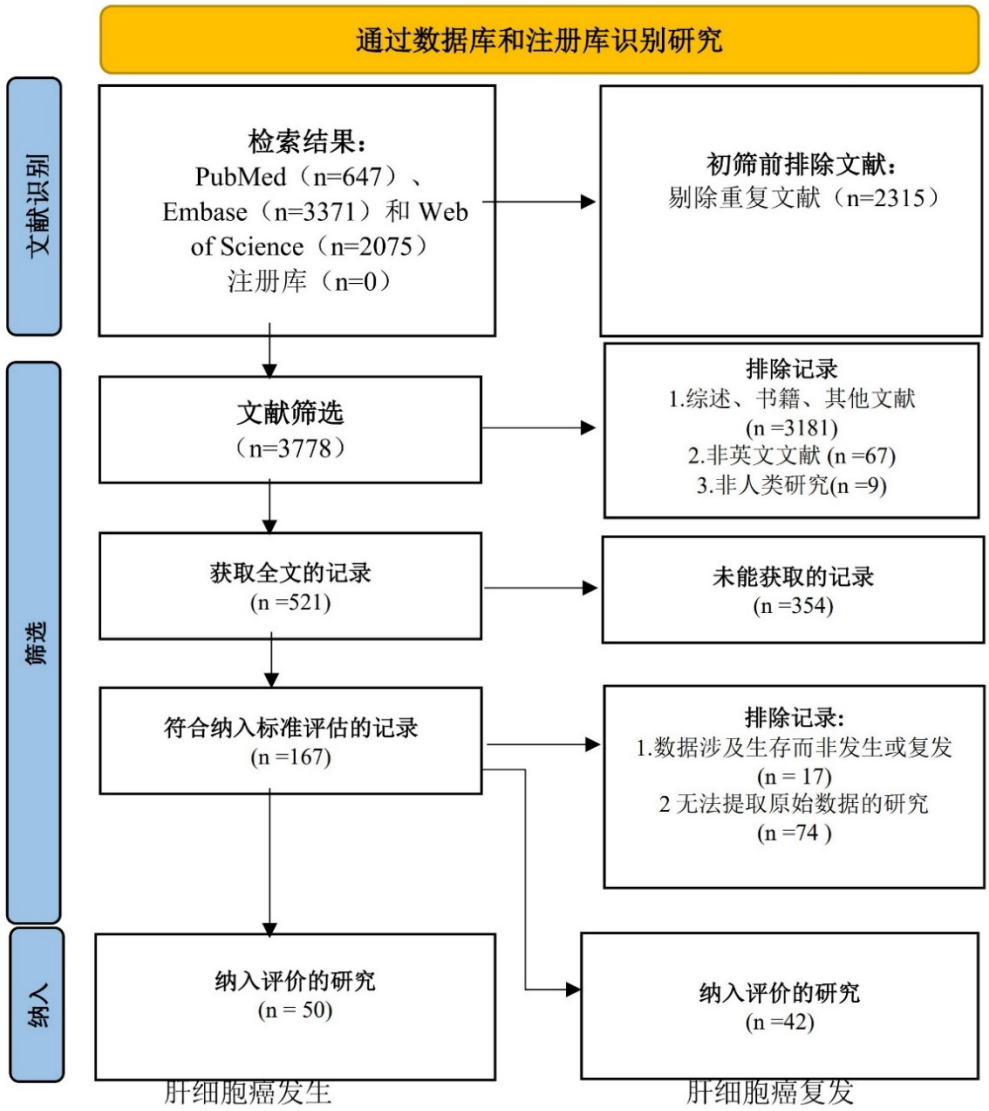

图 1　基于 PRISMA 2020 的流程图

表 1　纳入研究报告的直接作用抗病毒药物治疗后肝细胞癌发生特征

研究	国家	研究设计	设置	男性（%）	中位年龄	接受直接抗病毒药物治疗的患者数量	SVR（%）	肝细胞癌发生人数	肝细胞癌发生率（%）	随访开始	中位随访时间（月）	肝细胞癌发生时间（月）
Conti 2016[7]	意大利	前瞻性-回顾性	多中心	60.2-	63	285	91.6	9	3.16	EOT	6.0	-
Bielen 2017[15]	比利时	回顾性	多中心	62.7	59	355	60	4	1.1	EOT	6.0	6.0
Ida 2017[17]	日本	回顾性	单中心	46	72	74	100	5	6.7	EOT	15.0	
Kanwal 2017[19]	美国	回顾性	多中心	91	61	22,500	86.7	271	1.2	EOT	34.8	5.2
Kobayashi 2017[20]	日本	回顾性	单中心	44.2	63	77	100	2	2.6	EOT	48.0	-
Nagaoki 2017[21]	日本	回顾性	单中心	58	73	154	100	7	4.5	EOT	23.0	-
Ogata 2017[22]	日本	回顾性	单中心	42.1	67	1170	91	22	1.9	EOT	15.6	6.0
Ravi 2017[23]	美国	回顾性	单中心	62	60	66	92	6	9.1	DAAs	6.0	6.0
Ogawa 2017[31]	日本	前瞻性	多中心	43.3	66	1523	100	20	1.31	EOT	17.0	-
Calvaruso 2018[25]	意大利	前瞻性	多中心	52.9	65.4	2249	95.2	78	3.5	DAAs	14.0	9.8

Flisiak 2018[27]	波兰	前瞻性	多中心	55	55	194	-	4	2.1	EOT	2.0	15.0
Kuftinec 2018[29]	美国	回顾性	单中心	59	-	150	93	7	4.67	EOT	12.0	12.0
Masetti 2018[30]	罗马	回顾性	多中心	59.1	63	943	95.6	54	5.7	EOT	17.3	9.6
Ooka 2018[32]	日本	前瞻性	多中心	44.1	65.8	769	97.9	17	2.21	EOT	18.1	-
Romano 2018[33]	意大利	前瞻性	多中心	62.2	58.1	3,917	93.9	55	1.4	DAAs	1.46	-
Singer 2018[34]	美国	回顾性	多中心	36.02）	-	30183	-	433	1.43	DAAs	12.6	-
Akuta 2019[35]	日本	回顾性	单中心	42	66	1,922	100	43	2.24	EOT	28.8	12.0
Aziz 2019[36]	巴基斯坦	回顾性	单中心	59.7	55.1	300	93.4	10	3.33	EOT	6.0	-
Carrat 2019[37]	法国	前瞻性	多中心	56	57	7344	-	187	2.55	DAAs	33·4	-
Degasperi 2019[38]	意大利	回顾性	单中心	60	63	505	97	28	5.54	DAAs	25.0	11.0
Ide 2019[39]	日本	前瞻性	多中心	39.3	64.6	2552	100	70	2.7	DAAs	22.6	-
Idilman 2019[40]	土耳其	观察性	多中心	44	62	165	86	1	0.61	DAAs	22.1	-
Kogiso 2019[41]	日本	回顾性	单中心	50	65	304	96	3	1	DAAs	25.5	20.5
Lashen 2019[42]	埃及	回顾性	单中心	66.7）	56.1	342	93.6	26	7.6	EOT	15.0	10.6
Mun 2019[43]	美国	回顾性	多中心	-	-	33,876	-	991	2.93	DAAs	18.2	-
Piñero 2019[47]	拉丁美洲	前瞻性	多中心	47.7	58	1400	96.9	30	2.14	DAAs	16.0	7.9
Rinaldi 2019[49]	意大利	前瞻性	多中心	55.1	67	985	98.2	35	3.55	EOT	12.0	-
Watanabe 2019[51]	日本	回顾性	多中心	46.4	65.3	1212	96.9	35	2.89	EOT	18	-
Abe 2019[53]	日本	回顾性	多中心	48	65	1068	100	39	3.65	EOT	43.0	-
Buonomo 2020[54]	意大利	前瞻性	多中心	48.6	69	323	95.5	11	3.41	EOT	10.0	11.0
Chan 2020[55]	澳大利亚	回顾性	多中心	75.8	56	128	96.9	7	5.5	DAAs	23.8	13.0
Hassany 2020[57]	埃及	前瞻性	多中心	55.4	58.1	350	94	27	7.71	DAAs	24.0	-
Kanwal 2020[58]	美国	回顾性	多中心	96.5	61.6	18076	100	544	3.01	EOT	34.8	-
Sangiovanni 2020[62]	意大利	前瞻性	多中心	59	65	1161	96	48	4.13	DAAs	17.0	4.2
Shiha 2020[63]	埃及	前瞻性	多中心	52.4	-	2372	100	109	4.6	DAAs	23.6	-
Tani 2020[65]	日本	回顾性	多中心	50.1	68	1088	100	26	2.39	EOT	13.8	-
Tayyab 2020[66]	巴基斯坦	前瞻性	多中心	48.8	50	662	91.9	42	6.34	EOT	12.0	7.0
Hamoir 2021[69]	比利时	前瞻性	单中心	58	60.5	128	-	4	3.125	DAAs	13.0	12.0
Karbeyaz 2021[70]	瑞士	回顾性	单中心	61.2	-	263	94.3	19	7.22	DAAs	49.2	-
Minami 2021[71]	日本	回顾性	多中心	42	68	1,215	100	34	2.80	EOT	49.2	26.4
Muzica 2021[72]	罗马尼亚	前瞻性	多中心	45.5	60	479	100	23	4.8	EOT	60.1	19.6
Ridziauskas 2021[74]	立陶宛	回顾性	单中心	60	56.3	70	100	4	5.7	EOT	3.0	-
Azofra 2021[75]	西班牙	回顾性	多中心	59.9	57.2	506	100	5	0.99	DAAs	33.7	29.4
Caviglia 2022[77]	意大利	回顾性	单中心	57.6	65	575	100	57	9.9	EOT	44.9	29.3
Ogawa 2022[82]	日本	前瞻性	多中心	-	-	1760	100	86	4.89	DAAs	42.0	-
Salgado 2022[83]	墨西哥	回顾性	单中心	34.3	56.2	108	-	8	7.4	EOT	12.0	3.0
Tada 2022[84]	日本	回顾性	多中心	40.7	69.5	1070	100	54	5	BL	15.9	-
Yoo 2022[85]	韩国	前瞻性	多中心	-	-	91	100	5	5.5	DAAs	12.0	8.0
Hong 2023[86]	韩国	回顾性	单中心	39.3	59.1	873	100	44	5.04	EOT	44.4	-
Leal 2023[87]	巴西	前瞻性	多中心	40.5	60	1075	97.4	51	4.7	DAAs	40.3	17.9

HCC：肝细胞癌（hepatocellular carcinoma）；SVR：持续病毒学应答（Sustained virological response）；DAAs：开始 DAAs 治疗；EOT：直接抗病毒药物治疗结束的时间点；BL：基线；not available：不可用。

表 2　纳入研究报告直接作用抗病毒药物治疗后肝细胞癌复发的特征

研究	国家	研究设计	设置	男性（%）	中位年龄	接受直接抗病毒药物治疗的患者数量	SVR	NR	SVR（%）	随访开始时间	中位随访（月）	复发肝细胞癌人数	复发率	从肝细胞癌治疗到直接抗病毒药物治疗的平均时间（月）	发生肝细胞癌的平均时间（月）
ANRS CO22 HEPATHER[13]	法国	前瞻性	多中心	78	62	189	148	41	91.9	DAAs	20.2	24	12.9	-	-
ARNS CO12 CirVir[13]	法国	前瞻性	多中心	85	61	13	8	5	100	DAAs	21.3	1	7.7	-	16.5
ARNS CO23 CUPILT[13]	法国、比利时	前瞻性	多中心	82	61	314	248	66	96.8	DAAs	>12	7	2.2	67	70.3
Conti 2016[7]	意大利	前瞻性-回顾性	多中心	-	-	59	53	6	89.8	EOT	6	17	28.8	12.5	-
Reig 2016[14]	西班牙	前瞻性	多中心	69	66.3	58	-	-	97.5	DAAs	5.7	16	27.6	11.2	3.5
Bielen 2017[15]	比利时	回顾性	多中心	62.7	59	40	-	-	94.4	EOT	6	6	15	33	-
Cabibbo 2017[16]	意大利	前瞻性	多中心	60.1	70.4	143	-	-	96	DAAs	8.7	29	20.3	11	-
Ida 2017[17]	日本	回顾性	单中心	46	72	26	-	-	100	EOT	15	12	46.2	4.1	-
Ikeda 2017[18]	日本	回顾性	单中心	60	71	177	155	-	89.6	DAAs	20.7	61	34.5	55	-
Virlogeux 2017[24]	法国	回顾性	单中心	76	62	23	22	1	96	DAAs	35.7	11	47.8	7.2	13
Ogawa 2017[31]	日本	前瞻性	多中心	53.3	74	152	152	0	100	EOT	17	26	17.1	14.4	-
El Kassas 2018[26]	埃及	前瞻性	单中心	66	56.7	53	-	-	77.4	DAAs	16	20	37.7	-	-
Flisiak 2018[27]	波兰	前瞻性	多中心	55	55	10	-	-	-	EOT	24	3	30	-	-
Hassany 2018[28]	埃及	前瞻性	多中心	67.7	60.3	62	40	22	64.5	DAAs	12	26	41.9	9.4	
Masetti 2018[30]	罗马	回顾性	多中心	67.6	67	102	-	-	95.6	EOT	17.3	41	39	-	8.1
Ooka 2018[32]	日本	前瞻性	多中心	44.1	65.8	95	-	-	97.9	EOT	18.1	24	25.2		23
Degasperi 2019[38]	意大利	回顾性	单中心	62	72	60		-	97	DAAs	25	20	33.3	-	
Idilman 2019[40]	土耳其	观察性	多中心	60	65	35	-	-	86	DAAs	22.1	17	48.6	-	6
Kogiso 2019[41]	日本	回顾性	单中心	71	69	45	-	-	96	DAAs	25.9	15	33	16.3	11.6
Lashen 2019[42]	埃及	回顾性	单中心	92	56	50	50	0	100	EOT	15	14	28	5.18	4.5
Nagaoki 2019[44]	日本	回顾性	单中心	65.8	73	38	33	5	86.8	-	33	13	34	-	-
Nakano 2019[45]	日本	前瞻性	多中心	58.6	74.9	459	459	0	100	DAAs	29.4	217	47.2	-	34
Kinoshita 2019[46]	日本	回顾性	单中心	59	74.4	147	135	12	92	DAAs	21.6	80	54.4	-	-
Preda 2019[48]	罗马尼亚	回顾性	单中心	59.1	64	22	-	-	87.5	DAAs	44	6	27.2	23	24
Singal 2019[50]	美国和加拿大	回顾性	多中心	70.4	62.4	304	-	-	81.8	DAAs	10.4	128	42.1	5.8	13.2
Zou 2019[52]	美国	回顾性	多中心	98.9	66.6	264	-	-	92	DAAs	23.3	69	26.1	30.9	12.2
Chan 2020[55]	澳大利亚	回顾性	多中心	80	58	10	9	1	90	DAAs	23.8	5	50	3	8.8
Guarino 2020[56]	意大利	前瞻性	多中心	64.4	67.2	101	92	9	91.1	DAAs	31.7	31	30.7	10.1	-
Kuo 2020[59]	中国	回顾性	单中心	63.9	65.9	82	-	-	100	DAAs	<12	22	26.8	30.7	-
Lin 2020[60]	中国	回顾性	单中心	51.7	69.6	35	-	-	93.3	DAAs	20	13	37.1	24	21
Miuma 2020[61]	日本	回顾性	单中心	52.4	74	17	17	0	100	BL	>6	8	47.1	8.6	37.2
Sangiovanni 2020[62]	意大利	前瞻性	多中心	69	73	124	118	6	95	DAAs	16	40	32.3	11	7.7
Tanaka 2020[64]	日本	回顾性	单中心	78.6	69	28	-	-	100	DAAs	22.2	7	25	-	23.2
Ahn 2021[67]	韩国	回顾性	多中心	67	69.2	100	88	12	88	DAAs	15.8	37	37	-	-
Chen 2021[68]	中国	回顾性-前瞻性	多中心	39.3	70.7	107	104	3	97.2	DAAs	26.9	33	30.8	8.2	9.2
Hamoir 2021[69]	比利时	前瞻性	单中心	58	60.5	15	-	-	-	DAAs	13	2	13.3	-	12
Ochi 2021[73]	米兰	回顾性	多中心	55.4	71	56	56	0	100	-	40	19	33.9	5.6	-
Tani 2021[76]	日本	回顾性	多中心	63.8	75.5	130	-	-	-	EOT	41	83	63.8	-	-
Chen 2022[78]	中国	回顾性	单中心	54.2	65.2	48	48	0	100	EOT	19.6	5	10.4	41.2	-
Elbaz 2022[79]	埃及	回顾性	多中心	83.7	53.8	523	438	85	83.7	DAAs	39.8	105	20.1	-	28.7
Kuromatsu 2022[80]	日本	回顾性	多中心	58.6	71	70	70	0	100	DAAs	57.8	29	41.4	12	-
Ogawa 2022[81]	日本	回顾性	多中心	55.2	74	326	326	0	100	EOT	32.4	171	52.5	14.4	-

SVR：持续病毒学应答（Sustained virological response）；NR：无应答（No response）；DAAs：开始 DAAs 治疗；EOT：直接抗病毒药物治疗结束的时间点；BL：基线；not available：不可用。

3.2 肝细胞癌的发生率

随访结束时，合并肝细胞癌发生率为 3%（95%置信区间 3%-4%），异质性较高（I^2=93.5%）（图 2）。亚组分析显示，前瞻性队列研究和回顾性队列研究的肝细胞癌发生合并估计值相近（3%vs3%，p=0.68），随访时间小于或大于 12 个月的研究合并估计值也相近（3%vs3%，p=0.81）（图 S1 和图 S2）。然而，不同大陆的肝细胞癌发生率存在差异。非洲研究的肝细胞癌发生率为 6%（95%置信区间 4%-9%），大洋洲研究为 5%（95%置信区间 2%-9%），亚洲研究为 3%（95%置信区间 3%-4%），欧洲研究为 3%（95%置信区间 3%-4%），美洲研究为 3%（95%置信区间 2%-3%）。非洲和大洋洲的肝细胞癌发生率较高（p<0.043）（图 S3）。在所有亚组分析中，I^2值仍大于 50%，表明存在显著异质性。

7 项研究比较了接受直接抗病毒药物治疗的患者与接受干扰素治疗或未治疗患者的肝细胞癌发生率[20,21,34,37,70,71,85]（表 3）。4 项研究的多变量分析显示，接受直接抗病毒药物治疗的患者与接受干扰素治疗的患者之间的肝细胞癌发生率无显著差异[20,21,71,85]。1 项研究发现，与接受干扰素治疗相比，接受直接抗病毒药物治疗的患者肝细胞癌发生率显著增加，调整后的风险比为 6.62（95%置信区间 2.01-21.84，p=0.002）[70]。2 项研究显示，与未治疗的患者相比，接受直接抗病毒药物治疗的患者肝细胞癌发生率显著降低[34,37]。

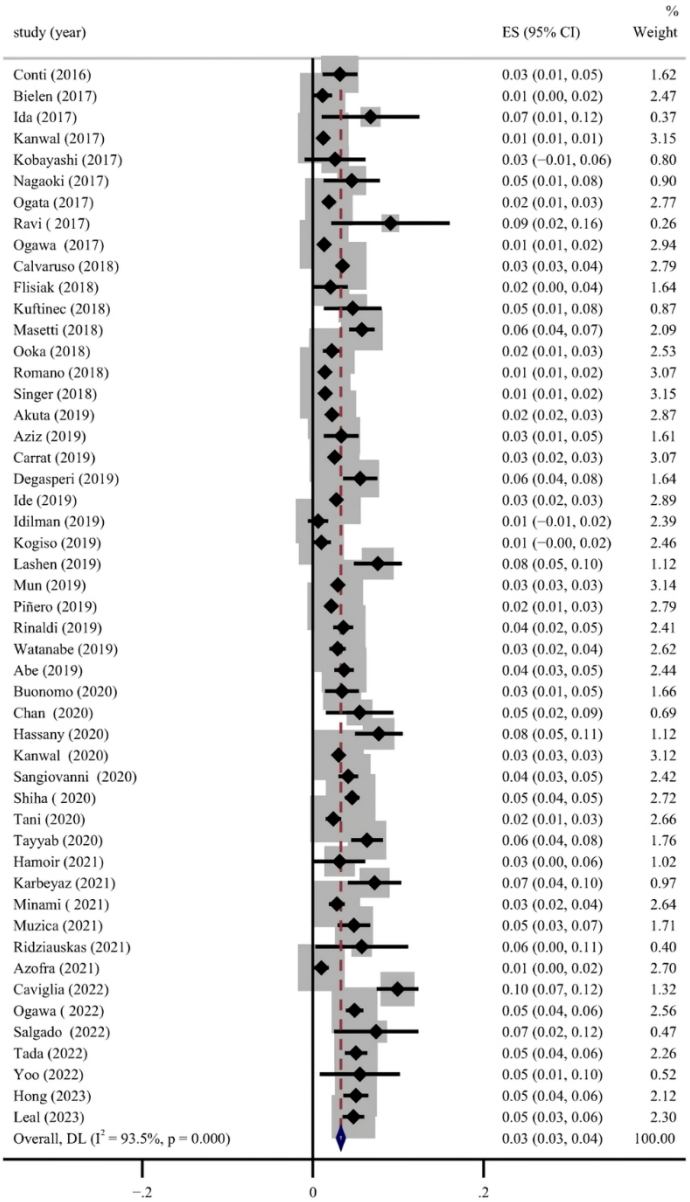

图 2　直接抗病毒药物治疗后肝细胞癌发生的患者比例

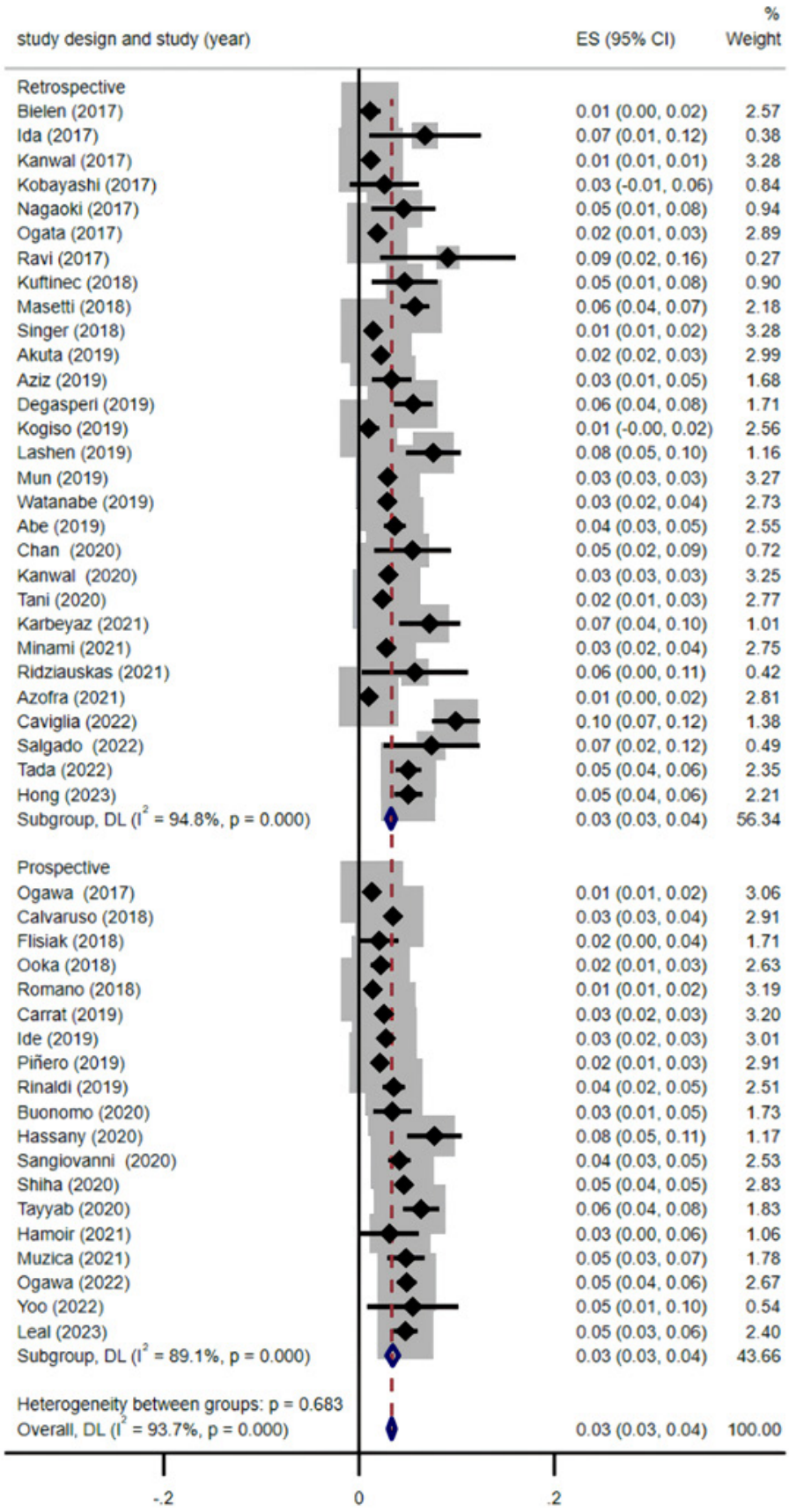

图 S1　直接抗病毒药物治疗后按研究设计（前瞻性或回顾性）分层的肝细胞癌发病率

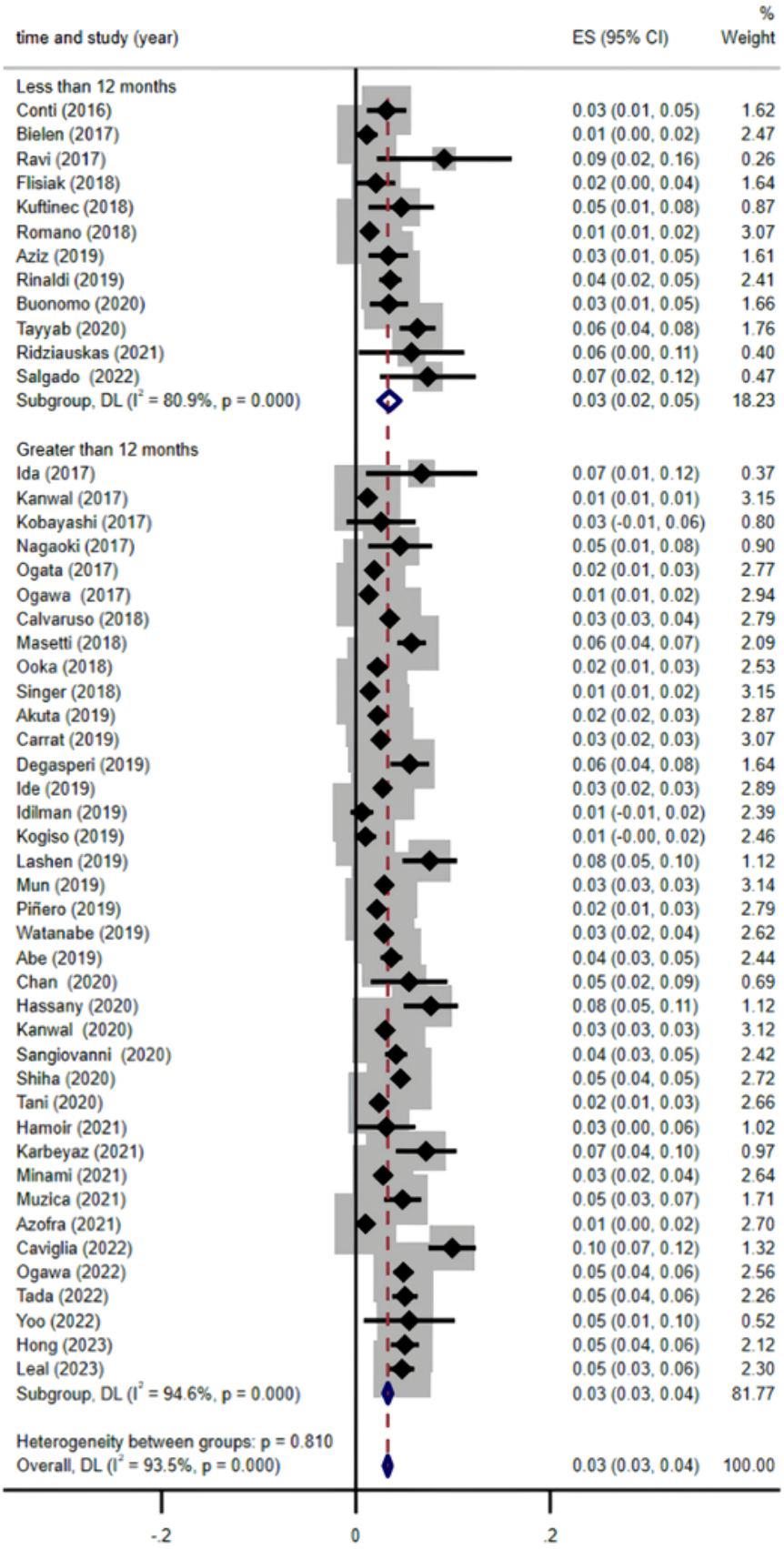

图 S2　按直接抗病毒药物治疗后随访时间分层的肝细胞癌的发病率

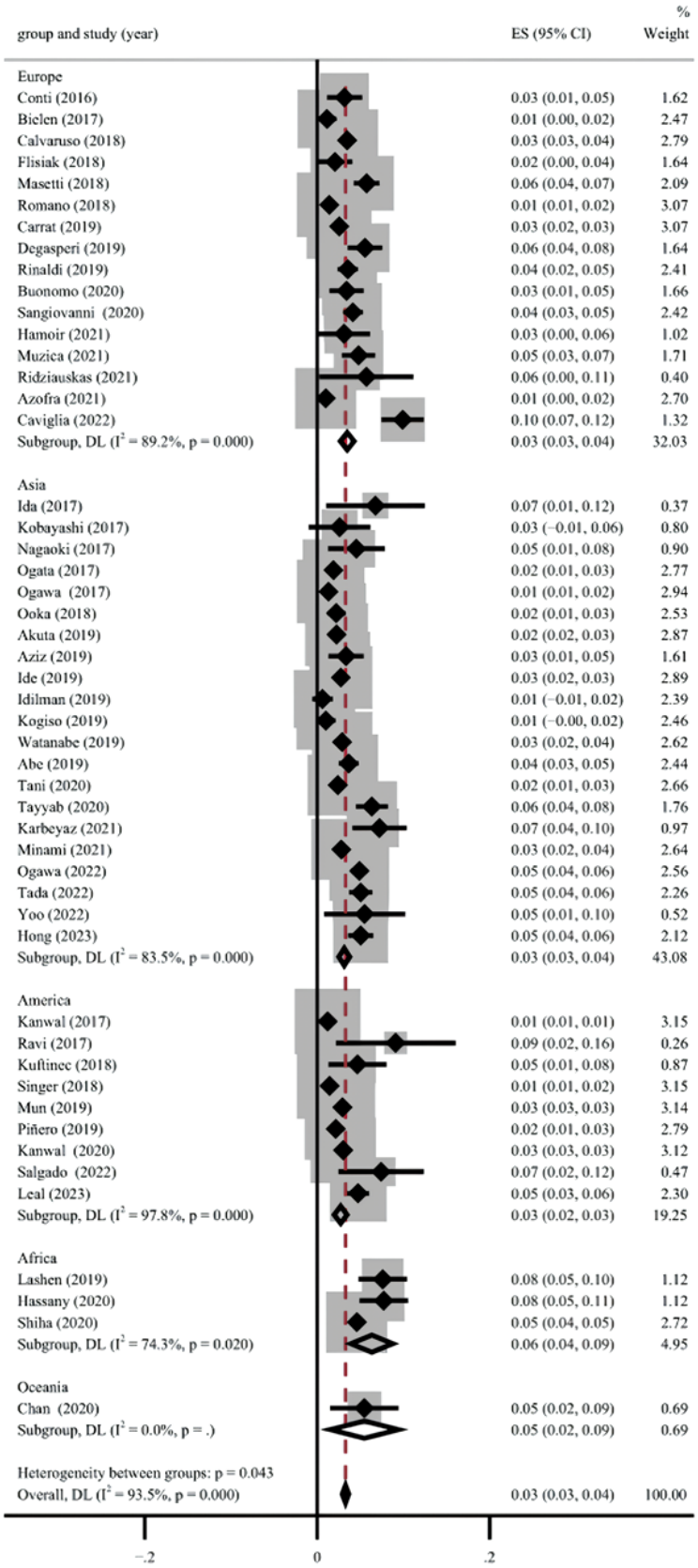

图 S3　直接抗病毒药物治疗后按研究地点分层的肝细胞癌的发病率

表 3　直接比较肝细胞癌发生率的研究特征

研究	国家	研究分组	患者数量	发生率比较
Singer 2018[34]	美国	接受直接抗病毒药物治疗与未接受治疗	30785/137502	在接受直接抗病毒药物治疗与未接受治疗的患者中，发生率分别为 1.18vs.0.64/100 人・月（校正风险比=0.84，95%置信区间 0.73-0.96）
Carrat 2019[37]	法国	接受直接抗病毒药物治疗与未接受治疗	7344/2551	接受直接抗病毒药物治疗与未接受治疗的患者中，发生率分别为 1.4vs.0.56/100 人・月（校正风险比=0.66，95%置信区间：0.46–0.93）
Kobayashi 2017[20]	日本	接受直接抗病毒药物治疗与接受干扰素治疗	77/528	接受直接抗病毒药物治疗与接受干扰素治疗的患者中，肝细胞癌发生率相似（校正风险比=0.529，95%置信区间 0.110-2.544，P=0.363）
Nagaoki 2017[21]	日本	接受直接抗病毒药物治疗与接受干扰素治疗	154/244	接受直接抗病毒药物治疗与接受干扰素治疗的患者中，发生率分别为 4.5%vs.5.3%（P=0.616 和 P=0.525）
Karbeyaz 2021[70]	瑞士	接受直接抗病毒药物治疗与接受干扰治疗	263/243	接受直接抗病毒药物治疗与接受干扰素治疗的患者中，发生率分别为 7.2%vs.7.4%（校正风险比=6.62，置信区间 2.01–21.84，P=0.002）
Minami 2021[71]	日本	接受直接抗病毒药物治疗与接受干扰治疗	1215/840	接受直接抗病毒药物治疗与接受干扰素治疗的患者中，发生率分别为 2.8%vs.4.9%（校正风险比=1.19，95%置信区间：0.61–2.33）
Yoo 2022[85]	韩国	接受直接抗病毒药物治疗与接受干扰素治疗	91/91	接受直接抗病毒药物治疗与接受干扰素治疗的患者中，发生率分别为 5.5%vs.5.4%

3.3 肝细胞癌的复发率

合并肝细胞癌复发率为 32%（95%置信区间 26%-38%），异质性较高（I^2=96.5%）（图 3）。亚组分析中，前瞻性队列研究和回顾性队列研究的肝细胞癌复发率分别为 25%和 36%（p=0.064）（图 S4）。随访时间小于或大于 12 个月的研究的肝细胞癌复发合并估计值相近（32%vs30%，p=0.69）（图 S5）。欧洲的肝细胞癌复发率最低，欧洲研究为 25%（95%置信区间 17%-33%），非洲研究为 31%（95%置信区间 19%-43%），美洲研究为 34%（95%置信区间 18%-50%），亚洲研究为 37%（95%置信区间 30%-44%），大洋洲研究为 50%（95%置信区间 19%-81%）（p=0.152）（图 S6）。在所有亚组分析中，I^2值仍大于 50%，表明存在显著异质性。

12 项研究比较了接受直接抗病毒药物治疗的患者与未治疗患者的肝细胞癌复发情况[13,24,48,50,59-61,64,73,78,80]（表 4）。5 项研究的多变量分析显示，接受直接抗病毒药物治疗的患者与未治疗患者的肝细胞癌复发率无显著差异。7 项研究发现接受直接抗病毒药物治疗的患者肝细胞癌复发率显著降低。在 6 项报告复发相对风险及 95%置信区间的研究中，接受直接抗病毒药物治疗的患者的合并复发风险低于未治疗患者（比值比 0.49，95%置信区间 0.27-0.88）（图 S7）。4 项研究比较了接受直接抗病毒药物治疗的患者与接受干扰素治疗的患者的肝细胞癌复发情况[44,46,59,68]（表 4）。3 项研究显示两组的肝细胞癌复发率无差异，1 项研究显示接受直接抗病毒药物治疗的患者肝细胞癌复发率显著降低。

3.4 研究质量和发表偏倚

大多数研究具有适当的队列代表性和暴露确定方法。然而，研究队列之间存在异质性，纳入患者的基线水平不同导致肝细胞癌发生或复发风险存在差异。在

肝细胞癌复发研究中，肝细胞癌完全缓解至开始直接抗病毒药物治疗的时间长度也存在异质性，这与肝细胞癌复发风险相关。纳入的大多数研究，无论是肝细胞癌发生还是复发研究，均为回顾性研究，被认为存在中等偏倚风险，且临床实践中可能存在监测不足的情况。此外，大多数研究主要通过医疗记录确定肝细胞癌的发生或复发，未记录影像学上的可疑结节。另外，部分研究随访时间较短或存在失访情况。总体而言，纳入研究的方法学质量被认为较低，研究质量评估的详细描述见表 S1 和表 S2。

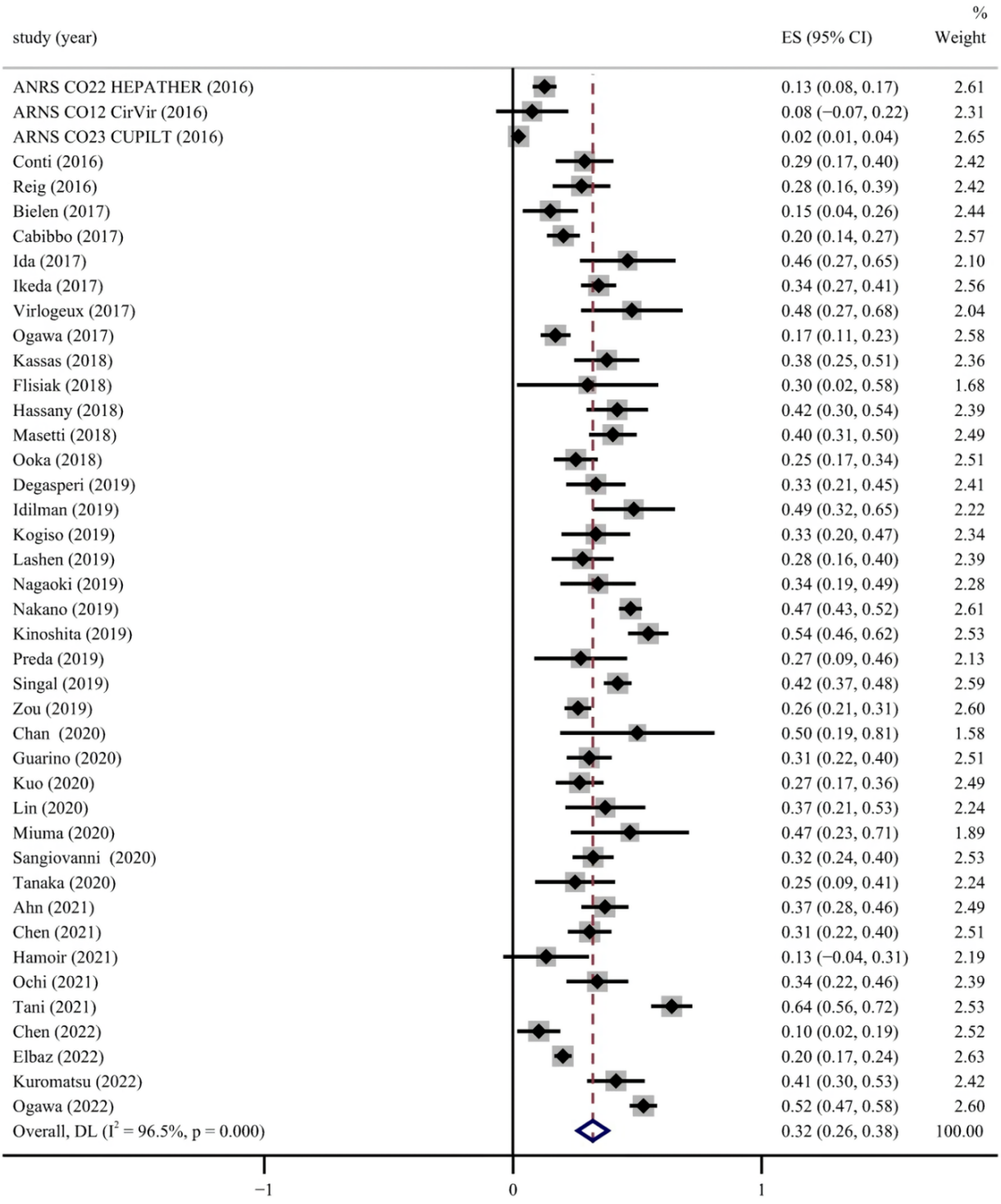

图 3　直接抗病毒药物治疗后肝细胞癌复发的患者比例

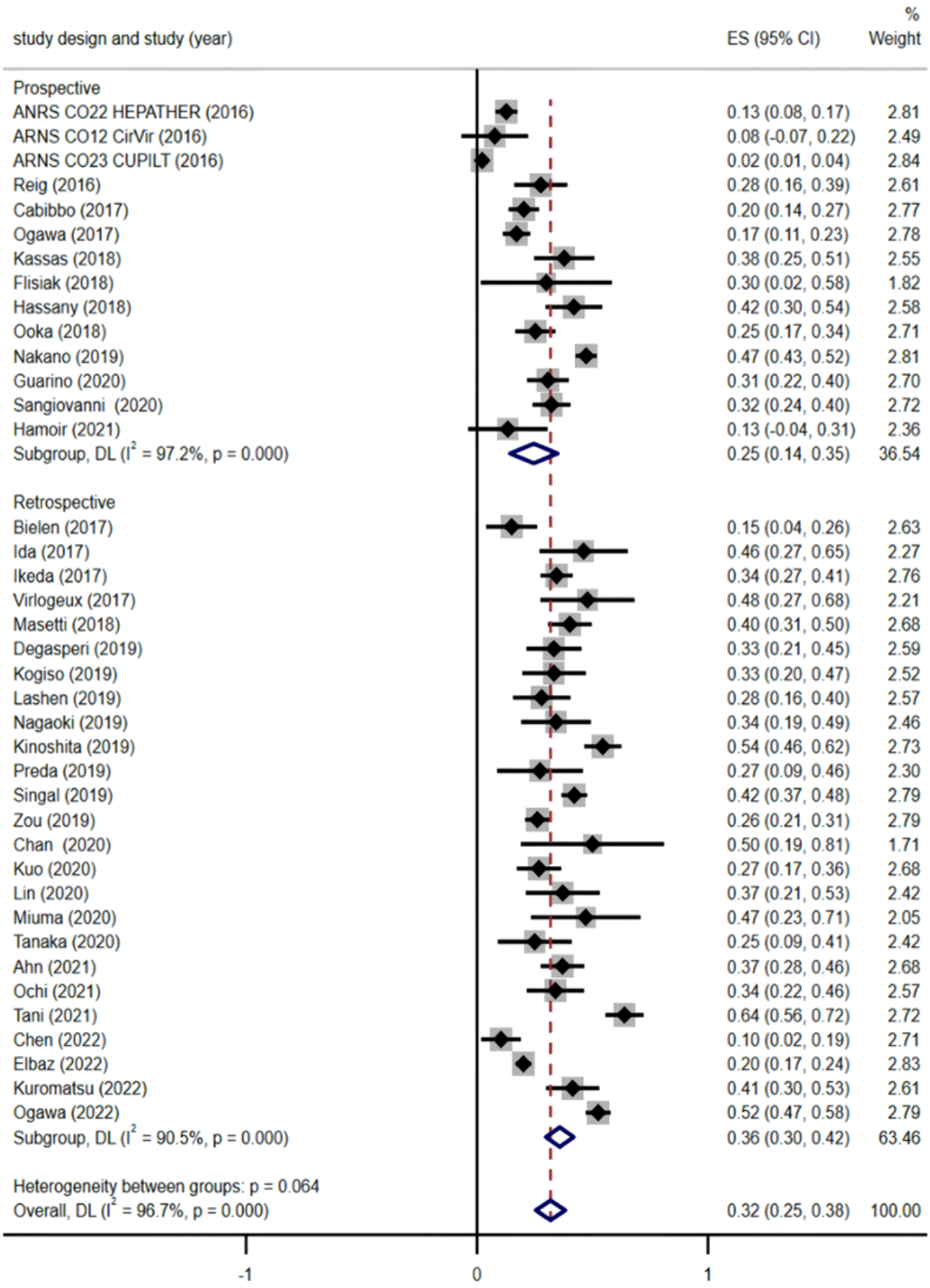

图 S4　直接抗病毒药物治疗后按研究设计（前瞻性或回顾性）分层的肝细胞癌的复发率

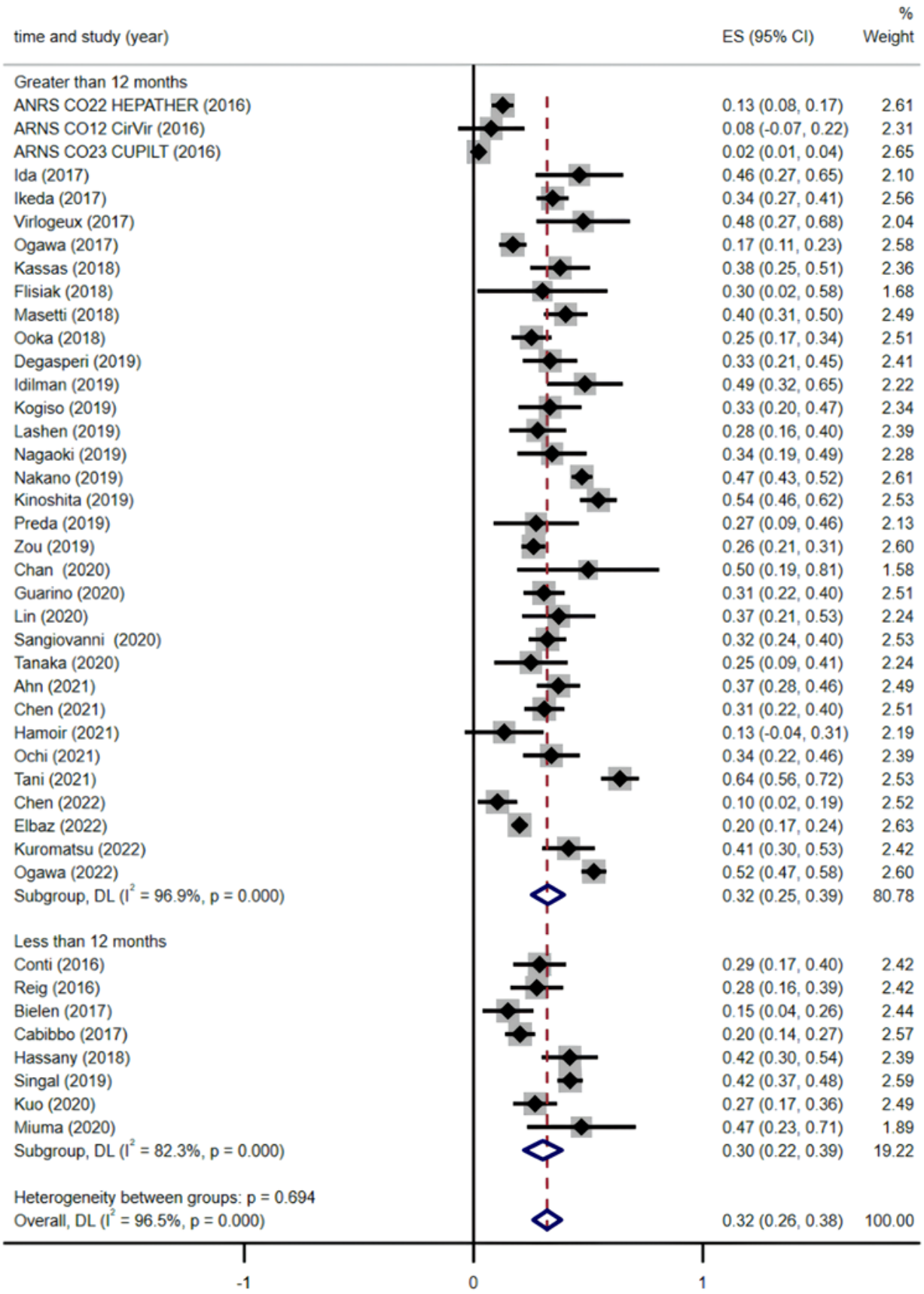

图 S5　直接抗病毒药物治疗后按随访时间分层的肝细胞癌的复发率

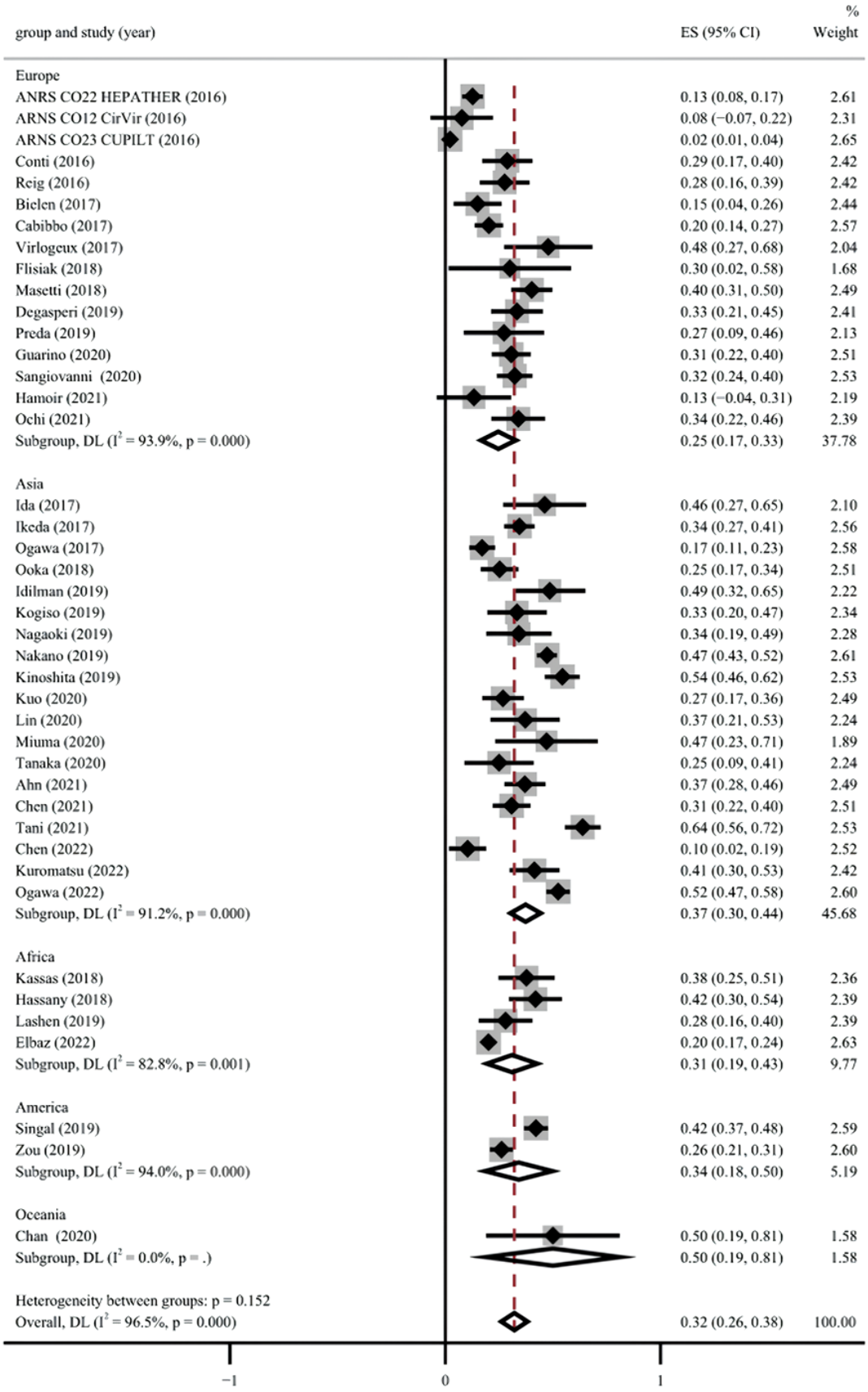

图 S6　直接抗病毒药物治疗后按研究地点分层的肝细胞癌的复发率

表 4　直接比较肝细胞癌复发率的研究特征

研究	国家	研究分组	患者数量	复发率比较
ANRS CO22 HEPATHER 2016[13]	法国	接受直接抗病毒药物治疗与未接受治疗	189/78	在接受直接抗病毒药物治疗与未接受治疗的患者中，发生率分别为 0.73vs.0.66/100 人·月（校正风险比 1.09，95%置信区间 0.55–2.16，*P*=0.8）。
ARNS CO12 CirVir 2016[13]	法国	接受直接抗病毒药物治疗与未接受治疗	13/66	在接受直接抗病毒药物治疗与未接受治疗的患者中，发生率分别为 1.11vs.1.73/100 人·月（校正风险比 0.41，95%置信区间 0.05–3.08，*P*=0.386）。
Virlogeux 2017[24]	法国	接受直接抗病毒药物治疗与未接受治疗	23/45	在接受直接抗病毒药物治疗与未接受治疗的患者中，发生率分别为 1.7vs.4.2/100 人·月（校正风险比 0.24，95%置信区间 0.10–0.55，*P*<0.001）。
Singal 2019[50]	美国和加拿大	接受直接抗病毒药物治疗与未接受治疗	304/489	复发率：在接受直接抗病毒药物治疗与未接受治疗的患者中分别为 42.1%vs.58.9%（校正风险比 0.90，95%置信区间 0.70–1.16）。
Kuo 2020[59]	中国	接受直接抗病毒药物治疗与未接受治疗	82/160	复发率：在接受直接抗病毒药物治疗与未接受治疗的患者中分别为 26.8%vs.58.5%（校正风险比 0.22；95%置信区间：0.12-0.42，*P*<0.001）。
Miuma 2020[61]	日本	接受直接抗病毒药物治疗与未接受治疗	17/59	接受直接抗病毒药物治疗与未接受治疗的患者在早期复发方面无差异。
Lin 2020[60]	中国	接受直接抗病毒药物治疗与未接受治疗	60/47	复发率：在接受直接抗病毒药物治疗与未接受治疗的患者中分别为 37.1%vs.45.8%（*P*=0.278）。
Tanaka 2020[64]	日本	接受直接抗病毒药物治疗与未接受治疗	28/28	复发率：在接受直接抗病毒药物治疗与未接受治疗的患者中分别为 25%vs.75%（*P*<0.001）。
Ochi 2021[73]	米兰	接受直接抗病毒药物治疗与未接受治疗	56/112	复发率：在接受直接抗病毒药物治疗与未接受治疗的患者中分别为 36.7%vs.66.7%（风险比 0.46；95%置信区间 0.27-0.77；*P*=0.003）。
Chen 2022[78]	中国	接受直接抗病毒药物治疗与未接受治疗	48/104	接受直接抗病毒药物治疗组的肝细胞癌累积复发率显著低于未治疗组（*P*<0.001）。
Kuromatsu 2022[80]	日本	接受直接抗病毒药物治疗与未接受治疗	56/56	在接受直接抗病毒药物治疗与未接受治疗的患者中，发生率分别为 11.5vs.16.5/100 人·月（*P*=0.0026）。
Preda 2019[48]	罗马尼亚	接受直接抗病毒药物治疗与未接受治疗	22/22	接受直接抗病毒药物治疗组的复发率显著低于未接受治疗组（*P*<0.05）。
Nagaoki 2019[44]	日本	接受直接抗病毒药物治疗与接受干扰素治疗	38/94	倾向评分匹配分析显示，接受直接抗病毒药物治疗组与接受干扰素治疗组之间无显著差异。
Kinoshita 2019[46]	日本	接受直接抗病毒药物治疗与接受干扰素治疗	147/156	接受直接抗病毒药物治疗组与接受干扰素治疗组的肝细胞癌复发率无显著差异（*P*=0.43）。
Kuo 2020[59]	中国	接受直接抗病毒药物治疗与接受干扰素治疗	82/80	经倾向评分匹配调整后，接受直接抗病毒药物治疗与接受干扰素治疗的患者的 1 年无复发生存率分别为 93.9%vs.81.4%（*P*=0.034）。
Chen 2021[68]	中国	接受直接抗病毒药物治疗与接受干扰素治疗	107/42	接受直接抗病毒药物治疗组与接受干扰素治疗组的肝细胞癌复发率无显著差异。

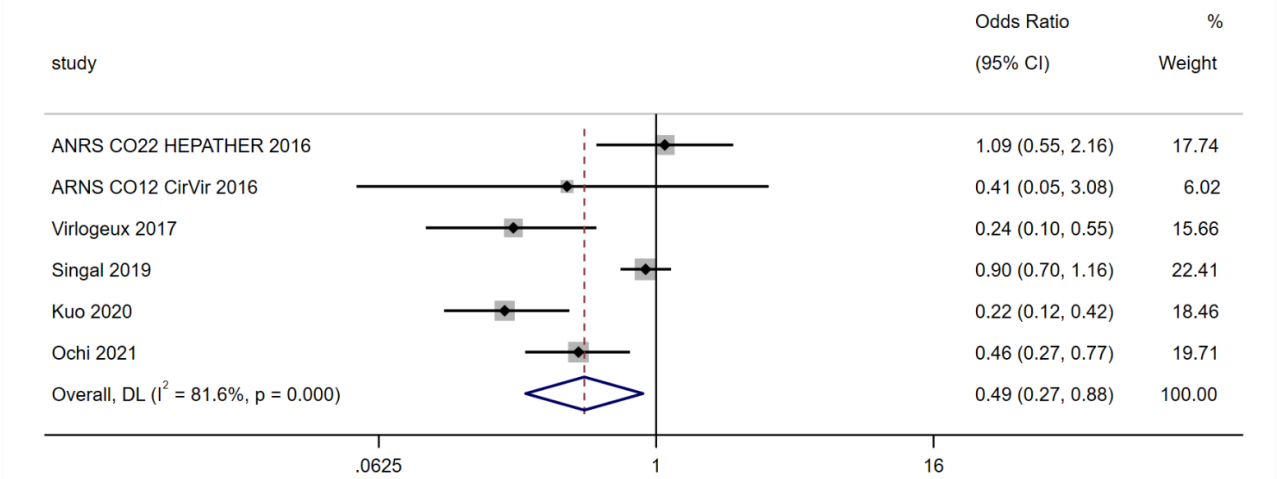

图 S7　直接抗病毒药物治疗组与未治疗组的复发相对风险

表 S1　基于纽卡斯尔-渥太华量表（NOS）的纳入研究肝细胞癌发生风险偏倚评估. * 表示低偏倚风险

研究	代表性队列	暴露因素确定	起点无结局事件	结局评估	随访周期	随访充分性
Study	Representative Cohort	Ascertainment of Exposure	Outcome Not Present at Start	Outcome Assessment	Follow-Up Period	Follow-Up Adequacy
Conti 2016	✳	✳	✳	Medium	High	Unknown
Bielen 2017	✳	✳	✳	High	✳	High
Ida 2017	✳	✳	✳	High	✳	Unknown
Kanwal 2017	✳	✳	✳	Medium	Unknown	Unknown
Kobayashi 2017	✳	✳	✳	Medium	✳	✳
Nagaoki 2017	✳	✳	✳	Medium	✳	✳
Ogata 2017	✳	✳	✳	Medium	✳	✳
Ravi 2017	✳	✳	✳	Medium	✳	✳
Ogawa 2017	✳	✳	✳	✳	✳	Unknown
Calvaruso 2018	✳	✳	✳	✳	✳	✳
Flisiak 2018	✳	✳	✳	High	✳	✳
Kuftinec 2018	✳	✳	✳	✳	Unknown	Unknown
Masetti 2018	✳	✳	✳	✳	✳	✳
Ooka 2018	✳	✳	✳	High	✳	High
Romano 2018	✳	✳	✳	✳	✳	✳
Singer 2018	✳	✳	✳	Medium	✳	✳
Akuta 2019	✳	✳	✳	Medium	✳	✳
Aziz 2019	✳	✳	✳	✳	High	Unknown
Carrat 2019	✳	✳	✳	✳	✳	✳
Degasperi 2019	✳	✳	✳	High	✳	✳
Ide 2019	✳	✳	✳	✳	✳	Unknown
Idilman 2019	High	✳	✳	High	✳	✳
Kogiso 2019	✳	✳	✳	High	Unknown	Medium
Lashen 2019	✳	✳	✳	✳	✳	✳
Mun 2019	✳	✳	✳	✳	✳	✳
Piñero 2019	✳	✳	✳	✳	✳	✳
Rinaldi 2019	✳	✳	✳	✳	✳	✳
Watanabe 2019	✳	✳	✳	Medium	✳	✳
Abe 2019	✳	✳	✳	Medium	✳	✳
Buonomo 2020	✳	✳	✳	✳	✳	✳
Chan 2020	High	✳	✳	High	✳	High
Hassany 2020	✳	✳	✳	✳	✳	✳
Kanwal 2020	✳	✳	✳	✳	✳	✳
Sangiovanni 2020	✳	✳	✳	✳	✳	✳
Shiha 2020	✳	✳	✳	✳	✳	✳
Tani 2020	✳	✳	✳	Medium	✳	✳
Tayyab 2020	✳	✳	✳	✳	✳	✳
Hamoir 2021	✳	✳	✳	✳	✳	✳
Karbeyaz 2021	✳	✳	✳	Medium	✳	
Minami 2021	High	✳	✳	✳	Unknown	Unknown
Muzica 2021	✳	✳	✳	✳	✳	✳
Ridziauskas 2021	✳	✳	✳	Medium	High	Unknown
Azofra 2021	✳	✳	✳	Medium	✳	✳
Caviglia 2022	✳	✳	✳	Medium	✳	✳
Ogawa 2022	High	✳	✳	High	✳	✳
Salgado 2022	✳	✳	✳	✳	✳	✳
Tada 2022	✳	✳	✳	✳	✳	✳
Yoo 2022	✳	✳	✳	✳	Unknown	Unknown
Hong 2023	✳	✳	✳	Medium	✳	✳
Leal 2023	✳	✳	✳	✳	✳	✳

表 S2　基于纽卡斯尔-渥太华量表（NOS）的纳入研究 HCC 复发风险偏倚评估. *表示低偏倚风险

研究	代表性队列	暴露因素确定	起点无结局事件	结局评估	随访周期	随访充分性
Study	Representative Cohort	Ascertainment of Exposure	Outcome Not Present at Start	Outcome Assessment	Follow-Up Period	Follow-Up Adequacy
ANRS CO22 HEPATHER 2016	✳	✳	Medium	High	✳	Unknown
ARNS CO12 CirVir 2016	✳	✳	Medium	High	✳	Unknown
ARNS CO23 CUPILT 2016	✳	✳	Medium	High	Unknown	Unknown
Conti 2016	✳	✳	Medium	Medium	High	Unknown
Reig 2016	✳	✳	✳	Medium	High	✳
Bielen 2017	✳	✳	High	High	✳	High
Cabibbo 2017	✳	✳	✳	✳	High	Unknown
Ida 2017	✳	✳	✳	High	✳	Unknown
Ikeda 2017	✳	✳	Medium	Medium	✳	✳
Virlogeux 2017	✳	✳	✳	High	✳	Unknown
Ogawa 2017	✳	✳	✳	✳	✳	Unknown
El Kassas 2018	✳	✳	High	High	✳	Unknown
Flisiak 2018	✳	✳	✳	High	✳	✳
Hassany 2018	✳	✳	✳	✳	✳	Unknown
Masetti 2018	✳	✳	✳	✳	✳	✳
Ooka 2018	✳	✳	High	High	✳	High
Degasperi 2019	✳	✳	High	High	✳	✳
Idilman 2019	High	✳	✳	High	✳	✳
Kogiso 2019	✳	✳	✳	High	Unknown	Medium
Lashen 2019	✳	✳	High	✳	✳	✳
Nagaoki 2019	✳	✳	✳	Medium	✳	✳
Nakano 2019	✳	✳	✳	✳	✳	✳
Kinoshita 2019	High	✳	✳	High	✳	
Preda 2019	High	✳	✳	High	✳	High
Singal 2019	✳	✳	Medium	✳	Medium	Unknown
Zou 2019	✳	✳	✳	✳	✳	High
Chan 2020	High	✳	✳	High	✳	High
Guarino 2020	✳	✳	✳	✳	✳	✳
Kuo 2020	✳	✳	✳	✳	Unknown	✳
Lin 2020	✳	✳	✳	✳	✳	✳
Miuma 2020	High	✳	✳	High	Unknown	Unknown
Sangiovanni 2020	✳	✳	✳	✳	✳	✳
Tanaka 2020	✳	✳	✳	Medium	✳	Medium
Ahn 2021	✳	✳	✳	✳	✳	✳
Chen 2021	✳	✳	✳	Medium	✳	Medium
Hamoir 2021	✳	✳	✳	✳	✳	✳
Ochi 2021	✳	✳	Unknowu	High	✳	Medium
Tani 2021	✳	✳	✳	✳	✳	✳
Chen 2022	✳	✳	✳	✳	✳	✳
Elbaz 2022	✳	✳	✳	✳	✳	✳
Kuromatsu 2022	✳	✳	✳	✳	✳	✳
Ogawa 2022	✳	✳	✳	✳	✳	✳

4 讨论

在本系统评价和 Meta 分析中，我们发现无肝细胞癌病史的慢性丙型肝炎患者接受直接抗病毒药物治疗后肝细胞癌的发生率为 3%。在有治愈性肝细胞癌病史且感染丙型肝炎病毒的患者中，接受直接抗病毒药物治疗后肝细胞癌的合并复发率为 32%。尽管基于较宽的置信区间和显著的临床异质性对研究结果进行解释，但没有证据表明直接抗病毒药物治疗与肝细胞癌的发生或复发相关。在亚组中，我们观察到肝细胞癌的发生或复发存在地理差异。欧洲的研究发生率或复发率最低，而大洋洲（澳大利亚）的研究发生率或复发率最高。这可能与丙型肝炎病毒基因型分布的地理差异有关。研究表明，丙型肝炎病毒 1 型与肝细胞癌发生风险增加相关[88]。同时，这也可能与大洋洲纳入的研究数量最少有关。

本 Meta 分析纳入的部分研究比较了接受直接抗病毒药物治疗的患者与接受干扰素治疗或未治疗的患者。根据未调整的分析，接受直接抗病毒药物治疗后肝细胞癌的发生或复发风险显著降低。但在控制混杂因素后，这种优势大多消失。因为两组在直接抗病毒药物治疗时机，是否达到持续病毒学应答，肝脏疾病损害程度和肝癌发生潜能方面存在差异。多变量方差分析显示，接受直接抗病毒药物治疗的患者与接受干扰素治疗的患者的肝细胞癌发生或复发率相近。与未治疗的患者相比，接受直接抗病毒药物治疗的患者肝细胞癌的总体发生或复发风险更低。然而，其中一项研究发现，与干扰素治疗相比，接受直接抗病毒药物治疗的患者肝细胞癌发生率显著更高[70]，这与直接抗病毒药物治疗组纳入了高肝细胞癌风险、年龄较大且患有肝硬化的亚人群有关。

关于直接抗病毒药物治疗的潜在风险和获益仍存在不确定性。持续病毒学应答是评估丙型肝炎病毒感染治愈的指标，定义为治疗结束后至少 12 周未检测到循环丙型肝炎病毒 RNA，与丙型肝炎病毒相关的全因死亡率显著降低相关[89]。研究表明，无论肝病分期如何，直接抗病毒药物的持续病毒学应答率超过 90%[90-92]。直接抗病毒药物治疗可减轻肝纤维化并改善肝功能不全。因此，直接抗病毒药物是目前降低晚期肝细胞癌复发风险最有前景的策略。然而，直接抗病毒药物可在短期内降低丙型肝炎病毒载量，触发免疫监测变化，促进肝细胞癌的发生或早期复发[8]。因此，随访时间对于评估直接抗病毒药物治疗对肝细胞癌风险的持久性至关重要。我们对丙型肝炎病毒患者的建议是：（1）根据个体化的临床和生物学特征尽早使用直接抗病毒药物；（2）对晚期肝病和高肝细胞癌风险的患者加强病毒清除后的监测。

与先前的研究结果[8,9]相比，本 Meta 分析纳入了更多的研究，使 Meta 分析结果更具说服力。另一方面，本研究对接受直接抗病毒药物治疗后肝细胞癌的发生率进行了统计分析。此外，排除混杂因素的影响后，本研究比较了接受直接抗病毒药物治疗的患者与接受干扰素治疗或未治疗的患者的肝细胞癌发生或复发率。然而，本 Meta 分析存在局限性。纳入的大多数研究质量较低，影响了我们估计结果的可信度；高度的异质性也影响了我们的主要结果。

5 结论

直接抗病毒药物治疗后肝细胞癌的发生或复发率是可接受的。我们建议对丙型肝炎患者尽早使用直接抗病毒药物，并对晚期肝病和高肝细胞癌风险的患者加强病毒清除后的监测。

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