

特异性抗体免疫组化法检测EGFR突变价值的meta分析

马晴 王竞 钟殿胜 宁超 刘畅 肖平

【摘要】背景与目的 已有的研究表明：表皮生长因子受体（epidermal growth factor receptor, EGFR）基因突变是非小细胞肺癌（non-small cell lung cancer, NSCLC）患者应用表皮生长因子受体酪氨酸激酶抑制剂（EGFR tyrosine kinase inhibitor, EGFR-TKI）治疗疗效的最重要的预测因子。EGFR基因突变的患者对于使用TKIs分子靶向药物治疗疗效更敏感。其突变检测对肺癌一线靶向治疗选择尤为关键。研究分析特异性抗体免疫组化法（immunohistochemistry, IHC）检测EGFR突变与DNA测序法比较的敏感度与特异度，明确该方法准确性及临床应用价值。方法 通过Pubmed数据库检索所有符合检索条件的文献，末次检索日期2013年3月26日，根据纳入和排除标准进行进一步筛选，采用诊断试验meta分析方法，分析特异性抗体免疫组化方法与DNA直接测序法对比的敏感度与特异度。结果 10篇文献纳入meta分析，L858R 1,679例，E746-A750del 1,041例，诊断比值比（diagnostic odds ratio, DOR）分别为225.17（95%CI: 55.67-910.69）和267.16（95%CI: 132.45-538.88）；SROC曲线AUC分别为0.948,4（SEAUC=0.014,4）和0.981,3（SEAUC=0.009,9），Q*统计量分别为0.888,3（SEQ*=0.019,2）和0.9397（SEQ*=0.019,1）。结论 以上两种特异性抗体IHC鉴别EGFR突变的特异度高，灵敏度较高，作为筛查突变方法可行性高，具有一定的临床应用价值。

【关键词】 免疫组化；DNA测序；表皮生长因子受体；Meta分析

Value of Immunohistochemical Staining with Mutation-specific Antibodies in Detecting EGFR Mutations: A Meta-analysis

Qing MA¹, Jing WANG², Diansheng ZHONG^{1,2}, Chao NING¹, Chang LIU¹, Ping XIAO¹

¹Department of Medical Oncology, Tianjin Medical University General Hospital, Tianjin 300052, China;

²Tianjin Lung Cancer Institute, Tianjin Medical University General Hospital, Tianjin 300052, China

Corresponding author: Diansheng ZHONG, E-mail: zhongdsh@hotmail.com

Qing MA and Jing WANG contributed equally to this paper.

【Abstract】 Background and objective It has been proven that epidermal growth factor receptor (EGFR) mutation is the most important predictive factor for determining the effect of EGFR tyrosine kinase inhibitors (TKIs) applied to non-small cell lung cancer (NSCLC) patients. The patients with EGFR mutations response better to TKIs. To detect EGFR mutation has been particularly essential to select first-line treatment for lung cancer patients. To research and analyze the sensitivity and specificity of immunohistochemistry (IHC) using mutation specific antibodies in detecting EGFR mutations compared with DNA sequencing, and further evaluate the accuracy and clinical application value of IHC. **Methods** All required articles in Pubmed database were searched. The deadline of retrieval was March 26, 2013. Then further screening the articles based on the inclusion and exclusion criteria. Meta analysis of diagnostic test was applied to analyze the sensitivity and specificity of IHC compared with DNA sequencing for the detection of EGFR mutations. **Results** Ten articles were included in the meta analysis, there were 1,679 samples in L858R group and 1,041 samples in E746-A750del group. The DOR were 225.17 (95%CI: 55.67-910.69) and 267.16 (95%CI: 132.45-538.88) respectively; the AUC of SROC were 0.948,4 (SEAUC=0.014,4) and 0.981,3 (SEAUC=0.009,9) respectively; the Q values were 0.888,3 (SEQ*=0.019,2) and 0.939,7 (SEQ*=0.019,1) respectively. **Conclusion** The specificity and sensitivity of IHC method using these two mutation-specific antibodies were relatively high. As a screening method for EGFR mutations, the IHC with mutation specific antibodies is of clinical value.

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马晴与王竞为共同第一作者

作者单位：300052 天津，天津医科大学总医院肿瘤科（马晴，钟殿胜，宁超，刘畅，肖平）；300052 天津，天津医科大学总医院，天津市肺癌研究所（王竞，钟殿胜）（通讯作者：钟殿胜，E-mail: zhongdsh@hotmail.com）

【Key words】 Immunohistochemistry; DNA sequencing; Epidermal growth factor receptor; Meta analysis

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表皮生长因子受体 (epidermal growth factor receptor, EGFR) 是一种跨膜受体酪氨酸激酶, 属于HER家族的一员。研究^[1]发现, EGFR在50%-90%的非小细胞肺癌 (non-small cell lung cancer, NSCLC) 患者中高表达, 参与肿瘤的血管新生、迁移和粘附过程, 其扩增和突变已被认为是肺部肿瘤发生的主要机制之一。研究^[2-4]表明, EGFR基因突变状态是决定EGFR酪氨酸激酶抑制剂 (tyrosine kinase inhibitor, TKI) 疗效最重要的预测因子。目前, 已经报道的EGFR基因突变类型大约有60种^[1], 包括外显子19的缺失、外显子18和21的单核苷酸的替换突变及20外显子的复制突变, 其中外显子21的L858R和外显子19的缺失突变占突变的绝大多数, 可达89%以上。

美国国立综合癌症网络 (National Comprehensive Cancer Network, NCCN) NSCLC指南中明确指出, 对于IV期非鳞NSCLC患者, 应先行EGFR基因突变检测, 如果存在EGFR基因突变, 治疗上优先推荐EGFR-TKI。

目前EGFR突变检测方法较多, 现有临床应用的方法中, 直接测序法和ARMS法应用较广。DNA直接测序法, 作为EGFR突变检测的金标准, 可以检测所有的突变分析的区域, 但其灵敏度较低, 样本要求高, 只能对含量大于30%的突变基因进行检测。ARMS法敏感, 流程速度快、简单, 数据分析要求低, 但仅能检测已知突变, 且试剂费用昂贵, 临床中推广有一定困难。2009年Yu等^[5]首次制备出了2种最常见的EGFR突变的特异性单克隆抗体——抗E746-A750缺失突变抗体和抗L858R点突变抗体, 并应用于福尔马林固定、石蜡包埋组织的免疫组织化学 (immunohistochemistry, IHC) 检测。IHC作为常规病理检查手段, 具有标本处理方法简单、快速, 价格便宜, 且可以在临床病理科进行。近年来多项临床独立研究^[6-15]应用特异性抗体检测NSCLC患者EGFR突变检测与直接测序法比较, 其敏感度44%-100%, 特异度85%-99%。本文通过meta分析判定IHC法诊断准确度及临床应用价值。

1 材料与方法

1.1 检索策略 计算机检索Pubmed、中国医院知识仓库医学专题全文数据库 (CNKI)、中国生物医学文献数据库 (CBM disc) 和万方数据库。检索时间: 2009年1月-2013

年2月。收集国内外公开发表的“关于特异性抗体免疫组化法检测EGFR突变价值”的文章。中文检索词为表皮生长因子受体突变、L858R点突变、抗体、E746-A750缺失突变、免疫组织化学法、非小细胞肺癌。英文检索词: epidermal growth factor receptor、EGFR、non-small cell lung cancer、NSCLC、E746-A750 deletion mutation、immunohistochemical method、L858R point mutation。

1.2 纳入与排除标准 研究类型: 使用EGFR突变特异性抗体L858R及E746-750del检测外显子21及外显子19突变情况, 同时应用检测金标准DNA直接测序法比较其敏感度特异度的文献纳入标准: ①研究类型为含有EGFR突变特异性抗体L858R及E746-A750del检测对NSCLC患者EGFR突变检测价值的前瞻性或回顾性研究; ②研究对象采用DNA直接测序为金标准, 文献需明确说明受试者病理类型; ③文章提供了特异性抗体免疫组化检测在各病例组的真阳性 (true positive, TP)、真阴性 (true negative, TN)、假阳性 (false positive, FP)、假阴性 (false negative, FN) 例数或通过文章提供的数据可以计算; ④每组病例数均>20; ⑤文献中EGFR突变检测采用统一可评价的IHC方法及标准 (IHC阳性定义: 10%以上肿瘤细胞胞膜染色定义为阳性, DNA直接测序标本均来自于NSCLC患者的FFPE标本)。

排除标准: ①IHC与其他检测方法 (如ARMS法) 比较, 而无直接测序法对照的文献, 主要因为ARMS法虽为常用临床检查方法, 敏感度特异度高但仅能检测已知突变, 对于IHC法阳性预测值 (positive predictive value, PPV) 和阴性预测值 (negative predictive value, NPV) 统计有一定影响; ②采用除以上两种特异性抗体进行免疫组化的检测; ③EGFR免疫组化无统一判定标准的文献; ④重复性实验中, 发表较早或样本量较小的文献排除。

1.3 数据提取 所有纳入研究均提取以下内容: ①研究人群基本情况; ②各个研究的对于特异性抗体免疫组化法检测EGFR突变筛选试验的真阳性、真阴性、假阳性和假阴性, 由2名作者按照上述标准独立纳入文献和提取资料, 而后交叉核对, 意见不一致时通过讨论解决。

1.4 数据处理和统计学分析 整理原始文献并摘录数据, 由2名作者独立输入数据, 用meta-Disc 1.4进行分析。用各研究精确估计量在受试者工作特征 (receiver operator

characteristic curve, ROC) 曲线平面所形成的图像是否呈典型“肩臂”状分布进行各研究间由阈值效应引起的异质性分析; 用 q 检验 (inverse variance chi-squared test) 进行异质性检验, 如果同质性好 ($P \geq 0.05, I^2 \leq 25\%$), 采用固定效应模型进行数据合并; 若存在异质性 ($P < 0.05, I^2 > 25\%$) 采用随机效应模型分析。对比特异性抗体免疫组化方法与DNA直接测序法比较的敏感度、特异度, 评判该方法的准确性。对各研究的原始数据 (真阳性、假阳性、真阴性及假阴性的例数) 进行整合, 分别计算L858R及E746-A750del特异性抗体免疫组化的平均敏感度、特异度、比值比及各自的95%可信区间 (confidence interval, CI)。采用Mose's constant线性模型拟合SROC曲线, 以诊断比值比 (diagnostic odds ratio, DOR)、曲线下面积 (area under curve, AUC) 和 Q 统计量评价免疫组化法对NSCLC患者EGFR突变诊断的准确度。以纳入meta分析的各研究的敏感度为Y轴, 以 (1-特异度) 为X轴绘制SROC曲线, 直观上评估诊断试验的准确性, 曲线越靠近左上角, 曲线下面积越大, 其诊断准确性越高。按照 $\alpha=0.05$ 的检验标准进行统计学判断。

2 结果

2.1 检索结果及纳入研究文献 通过设定的检索词进行初步检索, 共找到88篇文献。阅读文题和摘要排除62篇, 初步纳入文献26篇。进一步阅读全文, 排除未达到纳入标准的文献12篇, 重复文献2篇, 无法获得所需全部原始数据的文献2篇, 最终纳入文献共10篇, 如图1所示, 其中2篇仅涉及L858R抗体, 未涉及E746-A750del抗体的免疫组化。

2.2 纳入研究的基本特征 本文共纳入10项研究, E746-A750del免疫组化累计病例1,679例, L858R免疫组化累计病例1,041例, 各研究免疫组化例数、敏感度及特异度参见表1。

2.3 纳入研究的方法学质量评价, 结果见表2。

2.4 Meta分析结果

2.4.1 异质性检验 以DOR作为效应量, 分别分析L858R、E746-A750del免疫组化与直接测序的异质性, Q 检验显示Cochran- Q 分别为20.31和5.64, $P < 0.05, P > 0.05, I^2$ 分别为65.5%和0%, L858R抗体免疫组化研究间存在异质性, 故以下分析选用随机效应模型。E746-A750del免疫组化采用固定效应模型。

2.4.2 Meta分析 随机效应模型meta分析结果显示: 应用特异性抗体免疫组化方法的合并敏感度、特异度、阳性似然比 (positive likelihood ratio, PLR)、阴性似然比 (negative likelihood ratio, NLR) 和DOR比分别如图2-图6所示。

图2所示为E746-A750del和L858R对NSCLC诊断敏感度的森林图。E746-A750del鉴别NSCLC患者EGFR突变的平均敏感度为0.90 (95%CI: 0.84-0.94, $P=0.656, 5$), L858R的平均敏感度为0.65 (95%CI: 0.59-0.70, $P < 0.001$)。

图3所示为E746-A750del和L858R对EGFR突变诊断特异度的森林图。E746-A750del鉴别EGFR突变的平均特异度为0.95 (95%CI: 0.93-0.97, $P < 0.001$), L858R的平均特异度为0.99 (95%CI: 0.98-0.99, $P=0.001, 6$)。

图4所示为E746-A750del和L858R诊断EGFR突变的PLR分别为25.23 (95%CI: 6.74-94.44, $P < 0.001$) 和44.69 (95%CI: 19.57-102.06, $P=0.011, 2$)。

图5所示为E746-A750del和L858R诊断EGFR突变

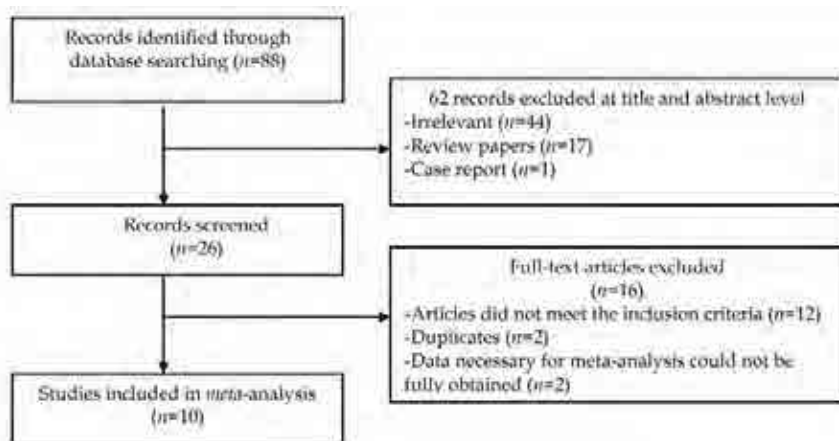


图1 文献筛选流程图

Fig 1 Flow chart for study selection

表1 纳入文献的基本资料及免疫组化方法的相关数据
Tab 1 General parameters of included studies and the data of IHC

Included studies	Country	Experimental methods	Age(yrs) [Median(range)]	n	L858R				E746-A750del							
					TP	TN	FP	FN	Sensitivity	Specificity	TP	TN	FP	FN	Sensitivity	Specificity
Brevet 2010 ^[6]	America	IHC, DNA sequencing	---	194	20	171	2	1	95	99	23	161	2	8	74	99
Kato 2010 ^[7]	America	IHC, DNA sequencing	59.9 (27-88)	70	9	7	0	2	82	100	9	56	2	3	75	97
Kitamura 2010 ^[8]	Japan	IHC, DNA sequencing	---	60	--	--	--	--*	79	100	--	--	--	--	83	100
Yu 2009 ^[5]	China	IHC, DNA sequencing	---	340	24	193	2	2	88	100	23	196	0	3	88	100
Wu 2011 ^[9]	China	IHC, DNA sequencing	65.2 (27.2-86.9)	143	38	77	23	5	88	77	29	9	1	2	94	90
Angulo 2012 ^[10]	Spain	IHC, DNA sequencing	60.1±8.9	136	--	--	--	--	89	100	--	--	--	--	100	100
Simonetti 2010 ^[11]	Spain	IHC, DNA sequencing	64 (36-85)	78	--	--	--	--	69	100	--	--	--	--	92	100
Nakamura 2010 ^[12]	Japan	IHC, DNA sequencing	---	20	5	10	5	0	100	67	3	15	2	0	100	88
Hofman 2012 ^[13]	France	IHC, DNA sequencing	---	61	--	--	--	--	90	99	--	--	--	--	--	--
Kozu 2011 ^[14]	Japan	IHC, DNA sequencing	---	577	--	--	--	--	44	100	--	--	--	--	--	--

*Values for TP, TN, FP and FN that did offered by the references can be calculated by related data. TP: true positive; TN: true negative; FP: false positive; FN: false negative; IHC: immunohistochemistry.

的NLR分别为0.13 (95%CI: 0.09-0.20, $P=0.770,5$) 和0.21 (95%CI: 0.12-0.39, $P<0.001$)。

图6所示为E746-A750del和L858R诊断EGFR突变的DOR分别为225.17 (95%CI: 55.67-910.69, $P=0.004,9$) 和267.16 (95%CI: 132.45-538.88, $P=0.775,6$)。

2.4.3 SROC曲线 由E746-A750del和L858R的SROC曲线, 计算灵敏度对数与(1-特异度)对数的Spearman相关系数

ρ , E746-A750del和L858R的 P 值分别为-0.500和0.382, P 均 >0.05 , 提示不存在阈值效应。SROC AUC两种检验方法分别为94.84%和98.13%, Q 值为0.888,3、0.939,7 (图7)。将每个研究逐一排除后行敏感性分析, 结果显示汇总灵敏度和特异度无明显改变, 提示meta分析结果的稳定性较好。

综上所述, E746-A750del和L858R特异性抗体免疫组

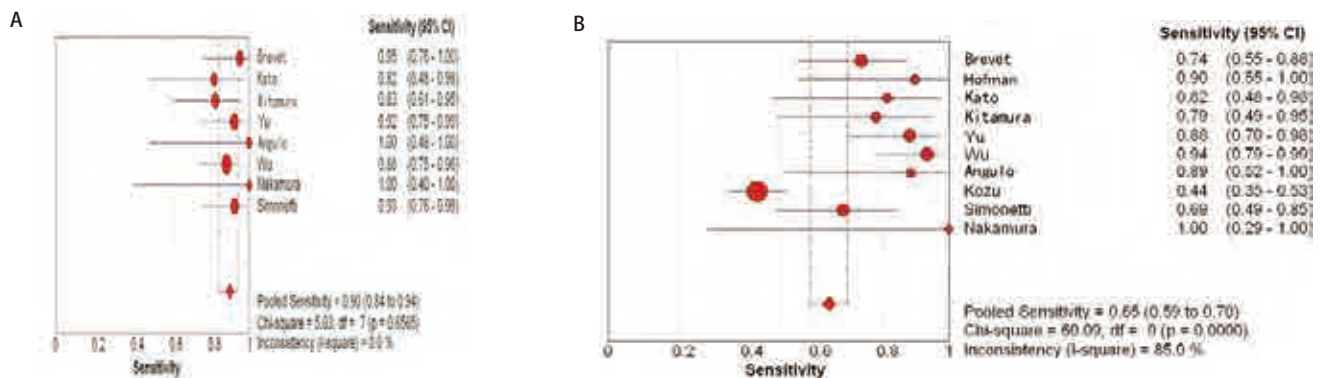


图2 E746-A750del (A) 和L858R (B) 敏感度森林图
Fig 2 The forest plots of E746-A750del (A) and L858R (B) sensitivity

表2 纳入研究的方法学质量评价

Tab 2 Methodological quality assessment of included studies

Included studies	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Brevet 2010 ^[6]	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
Kato 2010 ^[7]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Kitamura 2010 ^[8]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	Yes
Yu 2009 ^[5]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Wu 2011 ^[9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Angulo 2012 ^[10]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Unclear	No	No
Simonetti 2010 ^[11]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
Nakamura 2010 ^[12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Hofman 2012 ^[13]	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
Kozu 2011 ^[14]	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	No

1: Was the spectrum of patients representative of the patients who will receive the test in practice? 2: Were objectives pre-specified? 3: Is the reference standard likely to correctly classify the target condition? 4: Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? 5: Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis? 6: Did patients receive the same reference standard regardless of the index test result? 7: Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? 8: Was the experiment of index test clearly described and repeatable? 9: Was the experiment of reference standard clearly described and repeatable? 10: Were the index test results interpreted without knowledge of the results of the reference standard? 11: Were the reference standard results interpreted without knowledge of the results of the index test? 12: Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? 13: Were uninterpretable/ intermediate test results reported? 14: Were withdrawals from the study explained?

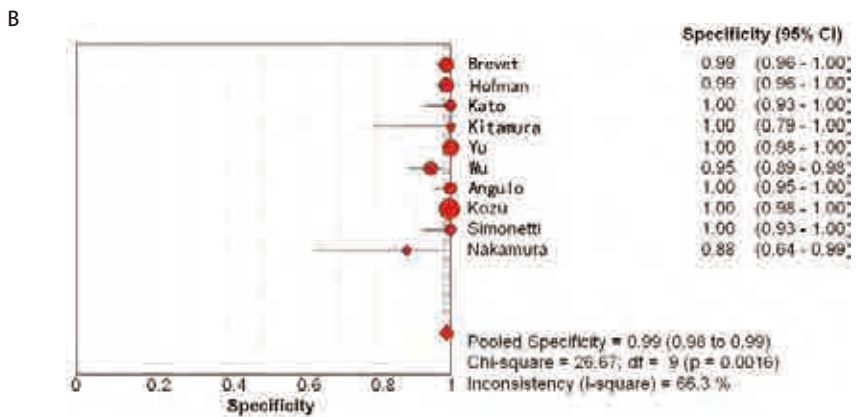
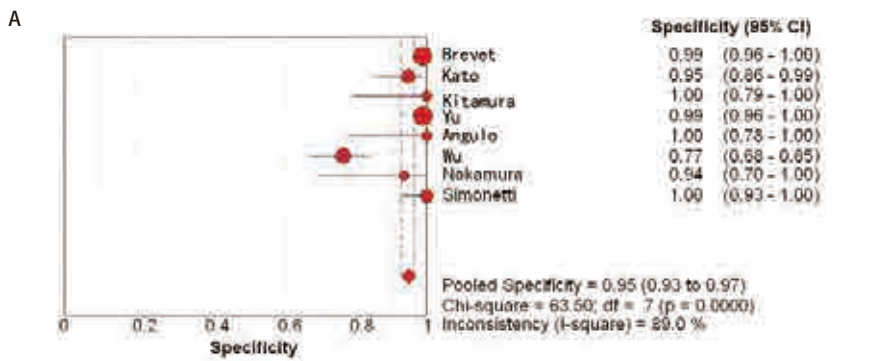


图3 E746-A750del (A) 和L858R (B) 特异度森林图

Fig 3 The forest plot of E746-A750del (A) and L858R (B) specificity

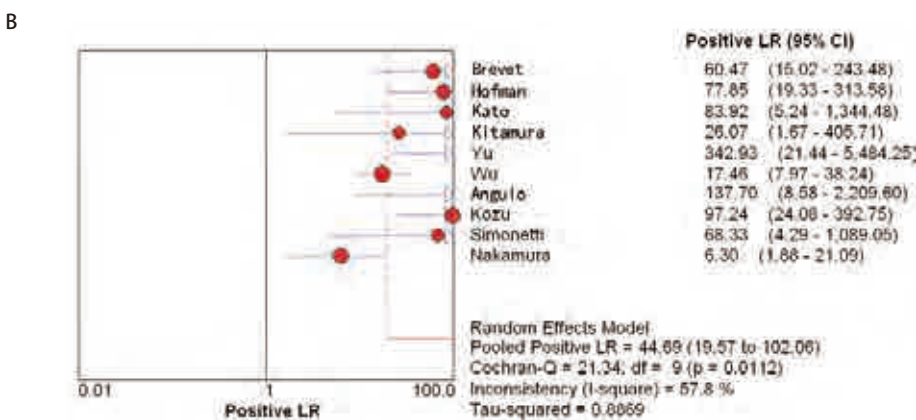
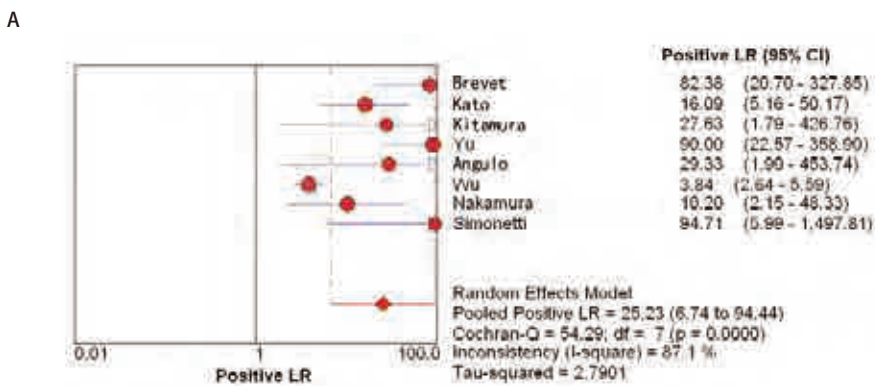


图4 E746-A750del (A) 和L858R (B) PLR森林图

Fig 4 The forest plot of E746-A750del (A) and L858R (B) PLR. PLR: positive likelihood ratio.

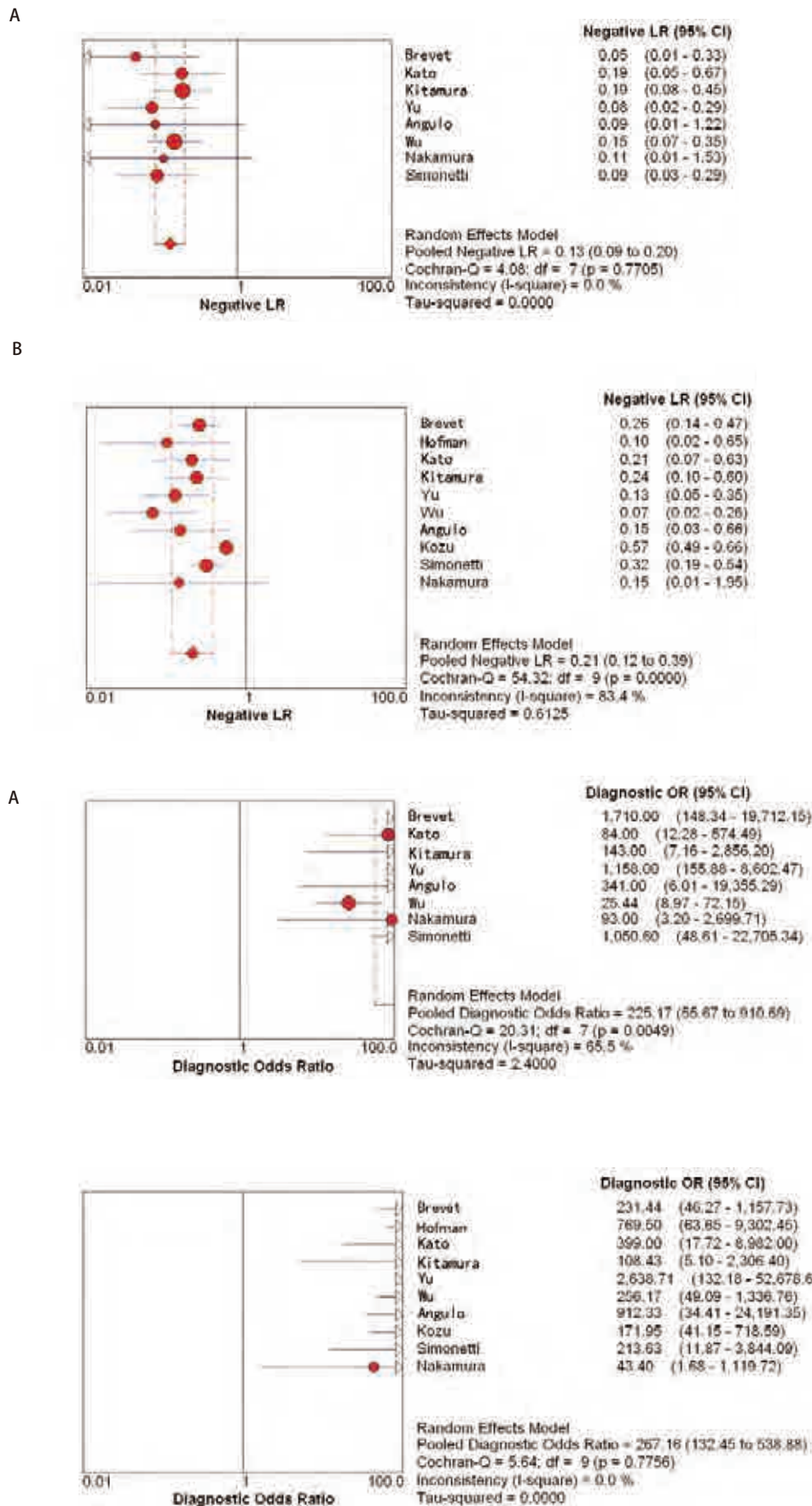


图 5 E746-A750del (A) 和L858R (B) NLP 森林图

Fig 5 The forest plot of E746-A750del (A) and L858R (B) NLP. NLR: negative likelihood ratio.

图 6 E746-A750del (A) 和L858R (B) DOR森林图

Fig 6 The forest plot of E746-A750del (A) and L858R (B) DOR. DOR: diagnostic odds ratio.

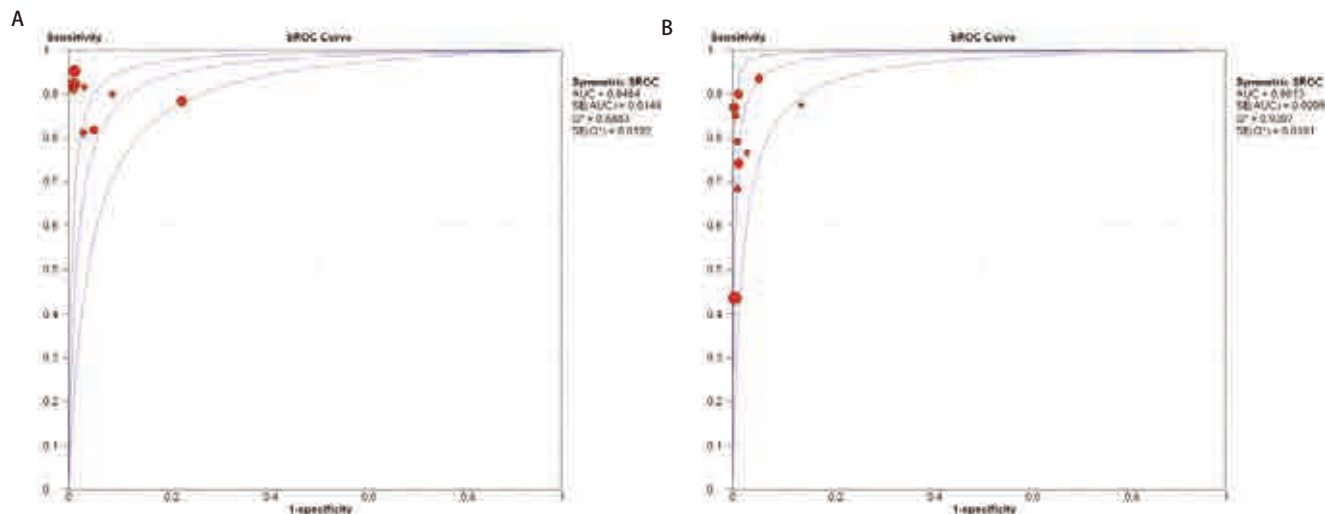


图7 E746-A750del (A) 和L858R (B) 的SROC曲线
 Fig 7 The SROC curve of E746-A750del (A) and L858R (B)

化法鉴别EGFR突变，方法可靠，特异度高，灵敏度较高，IHC方法作为筛查突变方法可行性高，具有临床应用价值。

3 讨论

本文对纳入的10项研究进行meta分析，通过合并诊断效应量、拟合SROC曲线比较L858R、E746-A750del特异性抗体免疫组化与直接测序法比较对EGFR突变的诊断效能。结果显示E746-A750del鉴别NSCLC患者EGFR突变的平均敏感度为0.90 (95%CI: 0.84-0.94)，平均特异度为0.95 (95%CI: 0.93-0.97)；L858R的平均敏感度为0.65 (95%CI: 0.69-0.70)，平均特异度为0.99 (95%CI: 0.98-0.99)。两者结果综合显示特异性较高而敏感性稍差，结合相关文献，考虑敏感度差别主要源于该方法仅能检测已知最常见E746-A750del和L858R突变，而不能检测其他EGFR基因突变，如9 bp、12 bp、18 bp、21 bp和24 bp缺失或L861Q替代等。Dahabreh等^[15]的一项meta分析报告显示，东亚人群中预测的特异性和敏感性分别为81%和81%。本研究结论与相关文献相符。

一般认为，PLR>10或NLR<0.1，基本可以确定或排除诊断。本研究得出的E746-A750del和L858R诊断EGFR突变的PLR分别为25.23 (95%CI: 6.74-94.44)和44.69 (95%CI: 19.57-102.6)，提示两者阳性均可以辅助临床医师做出相应判断，具有临床应用价值。但E746-A750del

和L858R的NLR分别为0.13 (95%CI: 0.09-0.20)和0.21 (95%CI: 0.12-0.39)，提示二者阴性时不能排除EGFR突变的可能。

DOR反映诊断试验的结果与疾病的联系程度。取值>1时，其值越大说明该诊断试验的判别效果较好；取值<1时，正常人比患者更有可能被诊断试验判为阳性；取值=1时，表示该诊断试验无法判别正常人与患者。本研究中E746-A750del和L858R诊断EGFR突变的DOR分别为225.17 (95%CI: 55.67-910.69)和267.16 (95%CI: 132.45-538.88)，提示诊断试验的判断效果好。

本文通过对可提供四格表数据的10篇文献，计算合并敏感度、特异度、PLR、NLR、DOR，行异质性分析后绘制SROC曲线，SROC曲线又名综合受试者工作特征曲线，不受异质性影响，可综合灵敏度与特异度信息，综合评价诊断试验的准确性，曲线以灵敏度为纵轴，以1-特异度为横轴，原理为通过TRP、FRP进行Logit变换将TRP与FRO间非线性关系转变为一种线性关系，利用最小乘法进行参数统计，建立SROC曲线回归方程并获得评价诊断试验准确度的统计量。分析本文SROC曲线显示，L858R和E746-A750DEL的AUC分别为0.948,4和0.981,3，Q*统计量分别为0.888,32和0.939,7，曲线靠近左上角，曲线下面积大，说明以上两种特异性抗体IHC鉴别EGFR突变的准确度均较高。本文纳入的研究间存在异质性，经Spearman相关系数检验，异质性与阈值效应无关，仍需做进一步做meta回归，寻找异质性的可能来源。

本次meta分析的局限性：①meta分析的局限性：检索到的文献不够全面。检索范围局限在已经发表的研究，对于未公开发表的研究，如会议论文无法获取，可能漏检一些灰色文献；检索语种局限于中文和英文，可能会漏检其它语种的相关研究；②纳入研究的局限性：特异性抗体IHC作为诊断性试验，采用盲法检测和盲法判断可尽量减少诊断的倾向性，而多数研究未报告是否采用盲法检测，存在测量偏倚的可能性。

综上所述，目前的IHC可以检测EGFR最常见外显子19缺失和21外显子L858R点突变这两种突变，其灵敏度与特异性与直接测序法比较无明显差别，且简单易行，具有一定临床应用价值，有望成为NSCLC患者EGFR突变检测的常规程序。

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