儿童哮喘专题

呼出气一氧化氮检测对儿童咳嗽变异性哮喘诊断价值的系统评价和meta分析

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［摘要］**目的**·采用系统评价和meta分析的方法评价呼出气一氧化氮（fractional exhaled nitric oxide，FeNO）检测对儿童咳嗽变异性哮喘（cough variant asthma，CVA）的诊断价值。**方法**·系统检索7个数据库（PubMed、Embase、Cochrane Library、Web of Science、中国生物医学文献服务系统、中国知网、万方数据库）建库至2022年3月1日的队列研究和病例对照研究。由2位研究人员分别独立根据纳入和排除标准对文献进行筛选，提取纳入文献中真阳性、假阳性、真阴性、假阴性的患儿人数以及FeNO的截断值。采用诊断性试验准确性质量评价工具2（diagnostic accuracy studies tool version 2，QUADAS-2）对纳入文献的风险偏倚和临床适用性2个方面进行质量评价。运用Revman 5.4软件绘制质量评价图。采用Stata 17.0统计分析软件的midas、spearman命令进行meta分析。采用灵敏度对数和（1－特异度）对数的Spearman相关系数检验阈值效应。采用双变量箱式图和I^2统计量评价研究间非阈值效应异质性。以双变量随机效应模型合并效应量。以Deek漏斗图评价发表偏倚。**结果**·共检索到1 099篇文献，经筛选最终纳入9篇。纳入的文献均有明确的专家共识或指南作为诊断标准。QUADAS-2评估结果显示纳入文献的质量较低。灵敏度和（1－特异度）的Spearman相关系数为0.05（P=0.90），表明无阈值效应引起的异质性。双变量箱式图及I^2=0的结果表明，研究间无明显的非阈值效应异质性。合并效应量结果显示，在慢性咳嗽患儿中，FeNO检测诊断CVA的灵敏度为0.82（95%*CI* 0.78~0.85），特异度为0.93（95%*CI* 0.89~0.95），阳性似然比为11.30（95%*CI* 7.40~17.10），阴性似然比为0.19（95%*CI* 0.16~0.24），诊断优势比为58（95%*CI* 34~101），综合受试者操作特征曲线（summary receiver operating characteristic curve，SROC曲线）下面积为0.89（95%*CI* 0.86~0.92）。Deek漏斗图显示不存在发表偏倚。**结论**·FeNO检测对儿童CVA的诊断价值呈中等程度。但受限于较低质量的原始研究证据，此结果需谨慎解读。

［关键词］呼出气一氧化氮；咳嗽变异性哮喘；儿童；诊断
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Diagnostic value of fractional exhaled nitric oxide in predicting cough variant asthma in children with chronic cough: a systematic review and meta-analysis

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[Abstract] Objective·To evaluate the values of fractional exhaled nitric oxide (FeNO) for the diagnosis of cough variant asthma (CVA) in children with chronic cough by systematic review and meta-analysis. **Methods**·PubMed, Embase, Cochrane Library, Web of Science, China Biology Medicine Database (SinoMed), China National Knowledge Infrastructure (CNKI), and Wanfang Database were systematically searched for cohort studies and case-control studies to March 1, 2022. Two researchers independently screened the studies according to the inclusion and exclusion criteria, and the number of true positive, false positive, true negative, and false negative patients and the cut-off value of FeNO were extracted from the studies. Diagnostic accuracy studies tool version 2 (QUADAS-2) was used to evaluate the quality of the included literature in terms of risk bias and clinical applicability. Revman 5.4

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was used to draw the quality evaluation chart. A meta-analysis was performed by the midas and spearman commands of Stata 17.0. Spearman correlation coefficients of sensitivity logarithm and (1－specificity) logarithm were used to test the threshold effect. The substantial heterogeneity caused by non-threshold effect was tested by bivariate box plot and I^2 statistic. The effect size was pooled by bivariate random effect model. Publication bias was evaluated by Deek´s Funnel plot. **Results**·One thousand and ninety-nine studies were retrieved in total and 9 were finally included. The diagnostic criteria of the included study were all from expert consensus or guidelines. The QUADAS-2 showed that the quality of the included study was low. The Spearman correlation coefficient of sensitivity and (1－specificity) was 0.05 (P=0.90), indicating that there was no heterogeneity caused by threshold effect. The results of bivariate box plot and I^2=0 showed that there was no heterogeneity caused by non-threshold effect. Combined effect showed that the sensitivity was 0.82 (95%*CI* 0.78—0.85), the specificity was 0.93 (95%*CI* 0.89–0.95), the positive likelihood ratio was 11.30 (95%*CI* 7.40–17.10), the negative likelihood ratio was 0.19 (95%*CI* 0.16–0.24), the diagnostic odds ratio was 58 (95%*CI* 34–101), and the area under the summary receiver operating characteristic (SROC) curve was 0.89 (95%*CI* 0.86–0.92). The result of Deek´s Funnel plot showed that there was no publication bias. **Conclusion**·FeNO test has a moderate diagnostic value in prediciting CVA in children with chronic cough. However, the results of the study need to be interpreted with caution due to the low quality of the original evidence.

[Key words] fractional exhaled nitric oxide (FeNO); cough variant asthma (CVA); child; diagnosis

咳嗽是儿童常见的就诊原因之一，咳嗽久治不愈不仅降低儿童的生活质量，也给家庭和社会带来沉重的经济负担[1-2]。多部国内外指南将儿童咳嗽持续时间大于4周定义为慢性咳嗽[3-6]。引起儿童慢性咳嗽的病因复杂多样，临床上明确慢性咳嗽的病因更加不易。国内一项多中心研究[7]显示，引起中国儿童慢性咳嗽最常见的三大原因为咳嗽变异性哮喘（cough variant asthma，CVA）、上气道咳嗽综合征（upper airway cough syndrome，UACS）、感染后咳嗽（postinfectious cough，PIC）。CVA是哮喘的一种特殊类型，以咳嗽为主要表现，无喘息、气促等症状，伴有明显的气道高反应性。嗜酸性粒细胞气道炎症是CVA重要的病理特征，确诊CVA往往需要诱导痰细胞学检查以及支气管激发试验[8-10]。然而诱导痰细胞学检查和支气管激发试验不仅对专业技术要求高，且需要患儿主动配合，在临床工作中普及难度较大。有研究[11]提示，约30%的CVA人群因得不到正规治疗最终发展为典型哮喘。因此，快速而准确地识别CVA，有助于儿童CVA的及时治疗。呼出气一氧化氮（fractional exhaled nitric oxide，FeNO）在越来越多的研究中被认为是嗜酸性粒细胞气道炎症的生物标志物；FeNO检测具有无创、便捷、敏感的优势，在监测气道炎症水平，预测糖皮质激素及Ⅱ类气道炎症相关单克隆抗体的治疗反应，评估其抗炎效果，预测疾病急性加重等方面发挥着重要作用[12]。目前临床上常规FeNO检测仪器所检测的是呼出气流速为50 mL/s时的eNO浓度，即$FeNO_{50}$（fractional concentration of exhaled nitric oxide at a 50 mL/s flow rate），简称FeNO[13]。已有多项针对成人的系统评价[14-17]显示，FeNO检测有助于区分CVA与健康人群以及其他病因导致的慢性咳嗽患者，且灵敏度和特异度均较高。然而，尚缺乏FeNO检测对儿童CVA诊断价值的循证证据。本研究旨在采用系统评价和meta分析的方法，总结现有相关研究证据，评价FeNO检测对儿童CVA的诊断价值，为临床应用提供循证依据。

1　资料与方法

1.1　文献纳入与排除标准

纳入标准：①研究类型为描述FeNO检测对儿童CVA诊断价值的队列研究或病例对照研究。②研究对象年龄≤18岁。③原始研究需明确提及采用诊断标准的来源。儿童CVA诊断标准依据国内和国外的权威专家共识或指南[18-20]，包括持续咳嗽大于4周，咳嗽为唯一或主要的症状，临床上无感染征象或者经较长时间抗生素治疗无效，经支气管舒张剂诊断性治疗咳嗽缓解，支气管激发试验阳性，有过敏性疾病史及过敏性疾病阳性家族史等。④分组为CVA患儿与其他病因导致的慢性咳嗽患儿。⑤文献可提取或者通过计算获取真阳性、假阳性、真阴性、假阴性的患儿人数，还可以提取或计算使用FeNO诊断儿童CVA的截断值。⑥在测量FeNO值前4周内未使用糖皮质激素、白三烯受体拮抗剂、抗组胺药等影响检查结果的药物。

排除标准：①会议摘要、个案报道、文献综述、信件，以及非中文、非英文文献。②研究对象合并有支气管扩张、慢性阻塞性肺疾病、闭塞性细支气管炎等疾病。③排除支气管哮喘相关的文献。④无法获取全文的文献。

1.2 文献检索

系统检索PubMed、Embase、Web of Science、Cochrane Library、中国生物医学文献服务系统（SinoMed）、中国知网（CNKI）、万方数据库共7个数据库。检索时间为建库至2022年3月1日。中文检索式以万方数据库为例，检索式为（咳嗽OR支气管炎）AND（FeNO OR呼出气一氧化氮OR一氧化氮呼气试验）AND（儿童OR儿科OR小儿OR新生儿OR婴儿OR幼儿OR青少年）。英文检索式以PubMed数据库为例，采用主题词加自由词检索方式：（"cough"［MeSH Terms］ OR "bronchitis"［MeSH Terms］ OR "cough*"［Title/Abstract］ OR "bronchitis"［Title/Abstract］ OR "bronchitic"［Title/Abstract］） AND（"nitric oxide"［MeSH Terms］ OR "FeNO"［Title/Abstract］ OR "eno"［Title/Abstract］ OR "nitric oxide"［Title/Abstract］） AND（"child"［MeSH Terms］ OR "pediatrics"［MeSH Terms］ OR "adolescent"［MeSH Terms］ OR "infant"［MeSH Terms］ OR "infant, newborn"［MeSH Terms］ OR "child*"［Title/Abstract］ OR "pediatric*"［Title/Abstract］ OR "paediatric*"［Title/Abstract］ OR "adolescent*"［Title/Abstract］ OR "infant*"［Title/Abstract］ OR "newborn*"［Title/Abstract］ OR "neonate*"［Title/Abstract］ OR "kid"［Title/Abstract］ OR "toddler*"［Title/Abstract］）。此外，为了尽可能全面地纳入文献，对相关综述、论著、会议摘要的参考文献进行手工检索和文献追溯。

1.3 文献筛选

由2位研究人员分别阅读文献题目和摘要，根据预先制订的纳入和排除标准进行初步筛选后，进一步阅读全文获得可纳入的文献。筛选过程中若出现意见分歧，则与第3位研究人员讨论解决。

1.4 资料提取

从文献中提取第一作者、研究发表时间、研究开展的国家或地区、研究设计方法、样本量、患儿年龄、FeNO的截断值、测量FeNO的仪器、诊断儿童CVA的标准，采用FeNO检测的真阳性、假阳性、真阴性以及假阴性患儿数量等内容。未能直接提取到FeNO检测诊断儿童CVA的截断值，则按约登指数=灵敏度＋特异度−1进行计算，取约登指数最大的值作为所对应的FeNO水平的截断值。以上工作由2位研究人员分别完成，如有意见分歧则由第3位研究人员仲裁。

1.5 文献质量评价

分别由2位研究人员独立使用诊断性试验准确性质量评价工具2（diagnostic accuracy studies tool version 2，QUADAS-2）[21]从风险偏倚和临床适用性2个方面对纳入的文献进行质量评价。风险偏倚包括“病例选择”“待评价诊断试验”“诊断金标准”“病例流程和诊断试验与金标准的时间间隔”4个领域，临床适用性包括“病例选择”“待评价诊断试验”“诊断金标准”3个领域，每个领域按照“高偏倚风险”“低偏倚风险”“不清楚”进行评估。评估结果如有分歧，则请第3位研究人员仲裁。采用Revman 5.4软件绘制质量评价图。

1.6 统计学分析

采用Stata 17.0软件的midas、spearman等命令完成统计学分析[22-24]。计算灵敏度对数和（1−特异度）对数的Spearman相关系数，探索阈值效应。如果两者呈正相关，则认为存在阈值效应。非阈值效应异质性检验采用双变量箱式图和I^2统计量评价。若I^2>50%，说明研究间存在高度异质性，则进一步探索异质性来源；否则，认为研究间不存在明显的异质性。以双变量随机效应模型合并效应量，获得合并的灵敏度、特异度、阳性似然比、阴性似然比、诊断比值比，及各指标的95%*CI*；绘制灵敏度和特异度的森林图和综合受试者操作特征（SROC）曲线图。绘制漏斗图，并以Deeks法判断是否存在发表偏倚，P<0.1表示差异有统计学意义。

2 结果

2.1 文献检索结果

通过系统检索，共获取相关文献1 099篇，剔除重复文献362篇，经阅读标题、摘要和全文后，最终纳入9篇。文献筛选的流程图如图1所示。

2.2 纳入文献的一般特征

如表1所示，纳入的9篇文献中，前瞻性研究5项，回顾性研究4项；8项研究来自我国，1项来自国外。所有研究都有明确的专家共识或指南作为诊断标准。

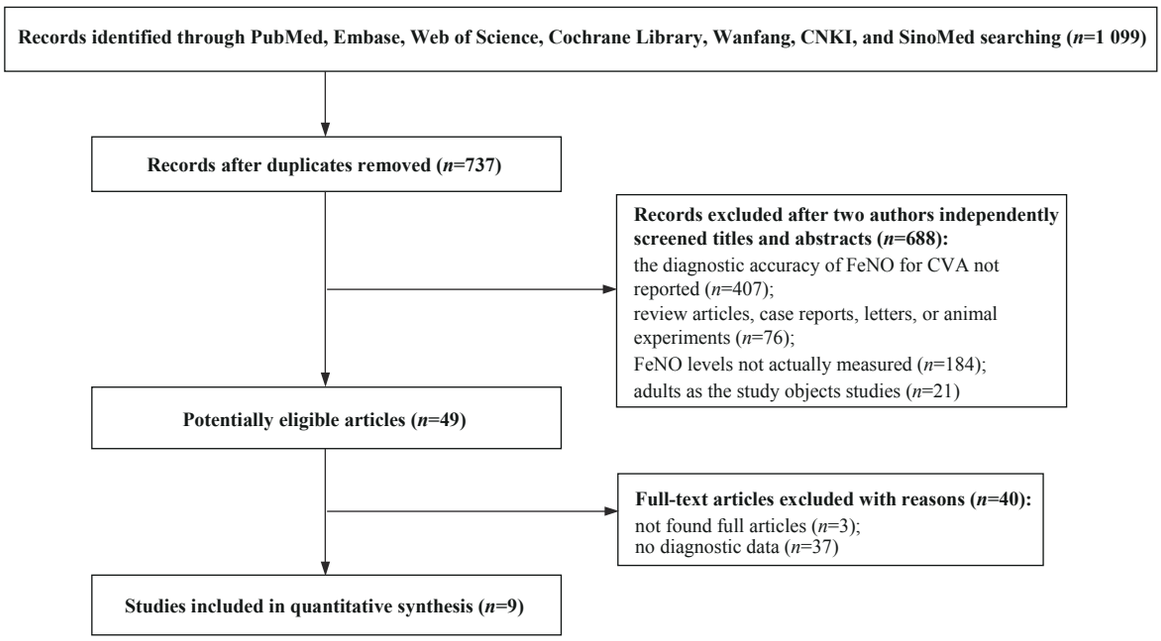


图1　文献筛选流程图

Fig 1　Flow diagram of study screening

表1　CVA与其他慢性咳嗽病因患儿的FeNO水平

Tab 1　FeNO levels of the CVA group and other children with chronic cough

Study	Country	Design	Sample size (CVA/nCVA)	Age/year	Cut-off value/ppb	FeNO measurement	Diagnostic criterion for CVA	FeNO test			
								TP/*n*	FP/*n*	FN/*n*	TN/*n*
JI et al, 2013[25]	China	Retrospective	42/44	5–14	22.5	NIOX MINO (Aerocrine, Sweden)	Chinese guideline for diagnosis and treatment of chronic cough in pediatrics (2008 version)[18]	37	4	7	38
CAO et al, 2015[26]	China	Prospective	81/127	0–12	36	Nano Coulomb Nitric Oxide Analyzer (Sunvou Medical Electronics Co., Ltd., China)	Chinese guideline for diagnosis and treatment of chronic cough in pediatrics (2008 version)[18]	68	4	13	123
ZHU et al, 2015[27]	China	Prospective	38/46	6–12	25.5	NIOX MINO (Aerocrine, Sweden)	Chinese guideline for diagnosis and treatment of chronic cough in pediatrics (2008 version)[18]	47	8	10	71
NIU et al, 2016[28]	China	Prospective	106/68	6–14	20.5	Nano Coulomb Nitric Oxide Analyzer (Sunvou Medical Electronics Co., Ltd., China)	Guideline for diagnosis and treatment of chronic cough in Chinese pediatrics (2013 version)[19]	79	9	27	59
ZHOU et al, 2018[29]	China	Prospective	53/62	6–14	25	NIOX MINO (Aerocrine, Sweden)	ACCP evidence-based clinical practice guideline (2006 version)[20]	45	2	8	60
YILDIZ et al, 2018[30]	Turkey	Retrospective	27/63	6–17	24	NIOX MINO (Aerocrine, Sweden)	ACCP evidence-based clinical practice guideline (2006 version)[20]	21	5	6	58
ZHOU et al, 2018[31]	China	Retrospective	41/65	6–13	27.64	NIOX MINO (Aerocrine, Sweden)	Guideline for diagnosis and treatment of chronic cough in Chinese pediatrics (2013 version)[19]	36	10	5	55
LI et al, 2018[32]	China	Retrospective	43/65	0–12	35	NIOX MINO (Aerocrine, Sweden)	Chinese guideline for diagnosis and treatment of chronic cough in pediatrics (2008 version)[18]	36	2	7	63
ZHU et al, 2019[33]	China	Prospective	57/79	6–12	25.5	NIOX MINO (Aerocrine, Sweden)	Guideline for diagnosis and treatment of chronic cough in Chinese pediatrics (2013 version)[19]	47	8	10	71

Note: 1 ppb =1×10^{-9} mol/L.　CVA—cough-variant asthma; nCVA—non-CVA; TP—true positive; FP—false positive; FN—false negative; TN—true negative.

2.3 文献质量评估

文献质量评估结果如图2所示。纳入的文献质量参差不齐，总体来说，文献质量不高，存在风险偏倚。在“病例选择”领域，没有文献明确说明所有的受试对象是否为连续或随机招募；在“待评价的诊断试验”领域，只有2篇文献采用了预先设定的界值，且大部分文献未明确说明金标准与待评价试验开展的顺序；在“病例流程和诊断试验与金标准的时间间隔”领域，仅2篇为低风险偏倚，但所有的文献都对“金标准”作了详细的描述。在临床适用性方面，几乎所有原始研究的“病例特征”“待评价的诊断试验”“金标准”都与本研究的研究问题相符，仅有1篇原始研究对所纳入对照组的病例特征解释不够明确。

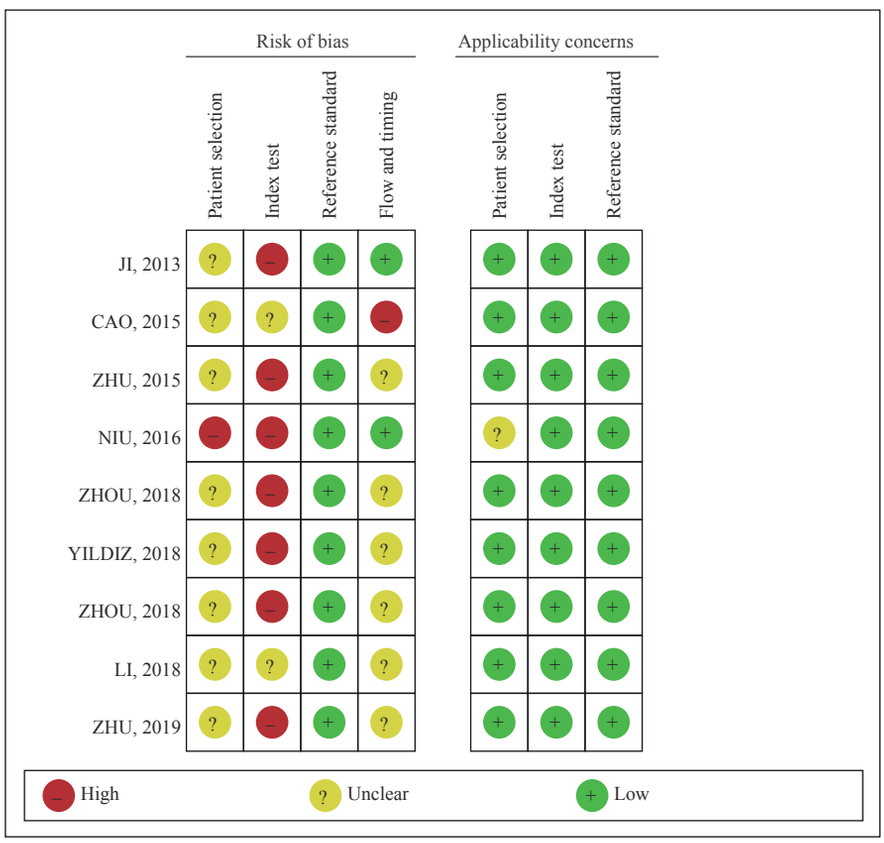


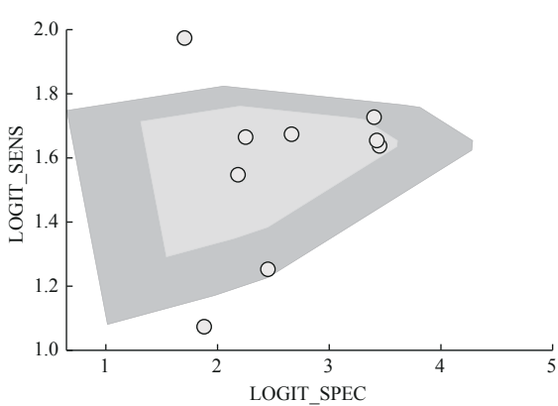
图2 纳入文献的质量评价

Fig 2 Quality assessment of the included studies

2.4 CVA与其他慢性咳嗽疾病患儿的FeNO水平

2.4.1 异质性检验 在阈值效应检验中，计算灵敏度对数和（1−特异度）对数的Spearman相关系数为0.05（P=0.90），表明两者无相关性，提示无阈值效应引起的研究间异质性。而在非阈值效应检验中，如双变量箱式图（图3）所示，大部分研究落在中间区域，只有2项研究落在双变量箱式图外面，且 I^2=0，说明纳入的研究间无明显异质性。

2.4.2 合并效应量 以双变量随机效应模型合并效应量。如图4、图5所示，在慢性咳嗽患儿中，FeNO检测诊断CVA的灵敏度为0.82（95%CI 0.78~0.85），特异度为0.93（95%CI 0.89~0.95），SROC曲



Note: SENS—sensitivity; SPEC—specificity.

图3 双变量箱式图

Fig 3 Bivariate boxplot

线下面积为0.89（95%*CI* 0.86~0.92）。阳性似然比为11.30（95%*CI* 7.40~17.10），阴性似然比为0.19（95%*CI* 0.16~0.24），诊断优势比为58（95%*CI* 34~101）。

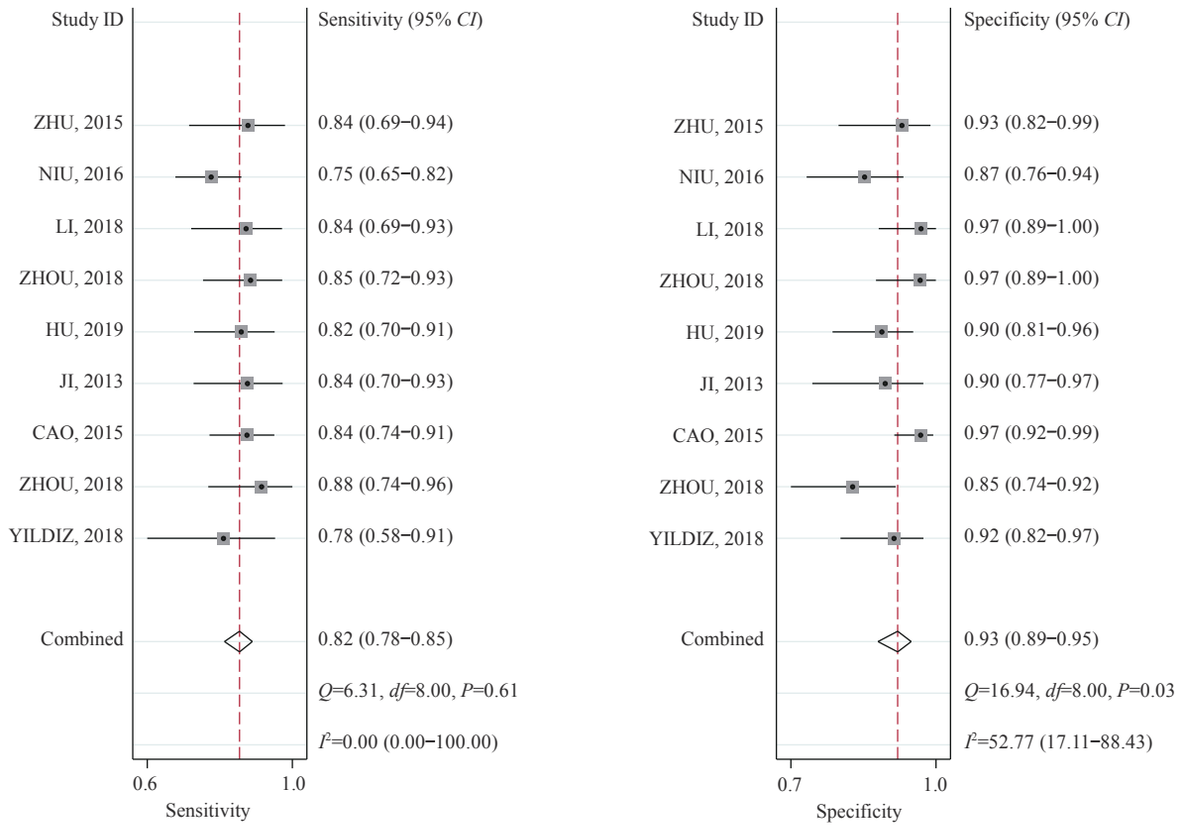


图4　敏感度和特异度森林图

Fig 4　Forest plot of sensitivity and specificity

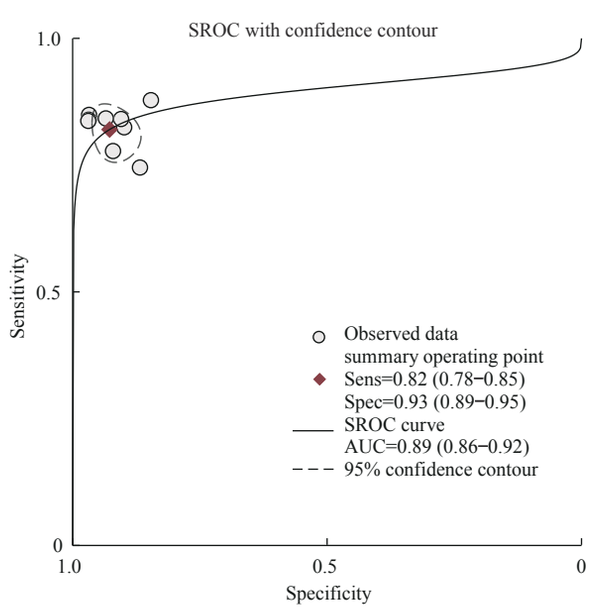
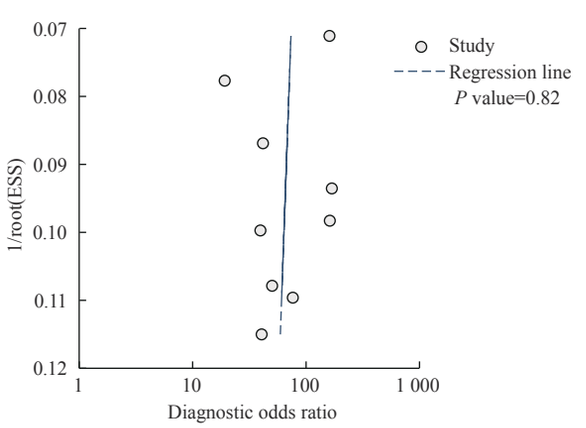


图5　FeNO在慢性咳嗽患儿中诊断CVA的SROC曲线

Fig 5　SROC curve on the diagnostic value of FeNO for CVA of children with chronic cough

2.4.3　发表偏倚　研究间发表偏倚检测通过Deek漏斗图呈现，图中直线左右两侧的点基本对称，且直线并未与*X*轴呈直角关系，定量检测提示*P*=0.82（>0.1），说明不存在发表偏倚（图6）。



Note: ESS—explained sum of squares.

图6　Deek漏斗图

Fig 6　Deek′s funnel plot

3 讨论

气道中的NO是由气道上皮细胞中的一氧化氮合酶催化*L*-精氨酸产生的一种生物介质。当气道受到外界刺激诱发Ⅱ类炎症时，可导致气道上皮细胞中的诱导型一氧化氮合酶表达增多，从而催化*L*-精氨酸产生大量NO从气道排出；而诱导型一氧化氮合酶的表达受白介素（IL）-4和IL-13调控，且这种炎症反应与激素敏感性密切相关。由此说明FeNO水平能较好地反映气道Ⅱ类炎症，预测糖皮质激素治疗效果[34-35]。近年来国内外制订了多项FeNO测定技术标准与临床应用指南[13, 36-37]，许多临床专家推荐该检测技术用于儿童慢性咳嗽、支气管哮喘以及婴幼儿喘息等疾病的诊疗。特别是对于无法配合肺功能检查的慢性咳嗽患儿，可通过测定FeNO协助诊断。

慢性咳嗽病因中的CVA主要表现为气道Ⅱ类炎症，其与典型哮喘有显著的不同。有研究[38]显示120例CVA患儿FeNO水平为19.0（13.0~24.0）ppb，而150例典型哮喘患儿的FeNO水平为33.5（23.75~56.5）ppb，两者差异有统计学意义（P<0.01），也说明CVA的气道炎症反应低于典型哮喘。由此，临床上评估分析FeNO检测在儿童典型哮喘中的诊断价值不适用于儿童CVA。本研究采用系统评价和meta分析的方法发现，FeNO检测对儿童CVA有中等程度的诊断价值。

纳入的9篇文献描述了CVA与其他病因导致慢性咳嗽患儿的FeNO水平。meta分析的结果表明，在慢性咳嗽患儿中，FeNO检测诊断CVA的诊断优势比为58，SROC曲线下面积为0.89，说明诊断效能较高；合并的效应量提示灵敏度0.82，提示漏诊率为18%；特异度为0.93，表明误诊率为7%；阳性似然比为11.30，说明FeNO诊断CVA患儿阳性的机会是其他病因导致慢性咳嗽患儿的11.30倍；阴性似然比为0.19，说明FeNO诊断CVA患儿阴性的机会是其他病因导致慢性咳嗽患儿的0.19倍。通过Deek漏斗图检测，说明研究之间不存在发表偏倚。从上述指标可以判断，FeNO测定有助于鉴别儿童CVA与其他病因导致慢性咳嗽的诊断。

本研究存在一定的局限性。首先，纳入的大部分研究在我国开展，缺少欧洲和美洲国家的相关研究，meta分析结果的适用性受到局限。其次，ZHOU等[29]和YILDIZ等[30]的研究中CVA诊断标准与纳入的其他研究不完全相同，此2项研究的诊断标准更加宽泛，但都包括对支气管舒张剂诊断性治疗有效。由于纳入文献较少，无法进行meta回归分析诊断标准的差异对结果的影响；但是从异质性检验、敏感度以及特异度的森林图初步推测这2项研究对meta分析的最终结果影响不大，未来需要纳入更多的研究来评估这一影响。最后，由于诊断性meta分析方法的局限，我们无法使用提取的数据合并得出FeNO检测诊断儿童CVA的截断值。

综上，通过现有的系统评价和meta分析发现，FeNO对儿童CVA有中等程度的诊断价值；综合患儿的临床特征以及其他实验室检查手段，FeNO检测对于评估气道炎症水平、鉴别CVA与其他原因导致的慢性咳嗽患儿有着重要的意义。然而需要指出的是，受限于较低质量的原始研究证据，本研究结果需要谨慎解读，亟待更多大样本、高质量的临床研究进一步论证FeNO在儿童CVA中的诊断价值，为疾病诊疗提供更加可靠的循证医学证据。

利益冲突声明/Conflict of Interests

所有作者声明不存在利益冲突。

All authors disclose no relevant conflict of interests.

作者贡献/Authors′Contributions

刘恩梅、党向阳参与试验设计；党向阳、唐雨一、李卫国参与检索策略的制订、数据提取及分析；刘恩梅、党向阳、唐雨一、李卫国参与文章的写作和修改。所有作者均阅读并同意了最终稿件的提交。

The study was designed by LIU Enmei and DANG Xiangyang. The development of search strategy, data extraction and analysis were performed by DANG Xiangyang, TANG Yuyi and LI Weiguo. The manuscript was drafted and revised by LIU Enmei, DANG Xiangyang, TANG Yuyi and LI Weiguo. All the authors have read the last version of paper and consented for submission.

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