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Research Article

Diagnostic Accuracy of Autofluorescence Bronchoscopy for Airway Inflammatory Changes in Studies for Cancer Detection: A Systematic Review and Meta-analysis

Jianrong Zhang[1]*, Jieyu Wu[2,3], Zhiheng Xu[4,5,6], Yujing Yang[7], Hua Liao[8] and Ziyan Liang[9]

[1]George Warren Brown School, Washington University in St. Louis, St. Louis, United States

[2]Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden

[3]Department of Pathology, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

[4]Department of Critical Care Medicine, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

[5]Guangzhou Institute of Respiratory Disease and China State Key Laboratory of Respiratory Disease, Guangzhou, China

[6]National Clinical Research Centre of Respiratory Disease, Guangzhou, China

[7]Department of Clinical Laboratory, Guangdong Academy of Medical Sciences and General Hospital, Guangzhou, China

[8]Department of Respiratory Medicine, The Fifth Affiliated Hospital of Southern Medical University, Guangzhou, China

[9]Department of Neonatology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

***Corresponding Author:** Jianrong Zhang, George Warren Brown School, Washington University in St. Louis, One Brookings Drive, St. Louis, MO, United States.

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Abstract

Background: Diagnostic accuracy of autofluorescence bronchoscopy (AFB) for early lung cancer has been sufficiently estimated, with high sensitivity but undesirable specificity. The aim of this systematic review and meta-analysis is to investigate its detection for airway non-normal lesions including inflammatory changes in studies for cancer detection.

Methods: A systematic review was performed in Web of Science and PubMed, according to the inception date of these databases to 31 December 2017. Eligible studies should have a direct comparison between AFB and conventional white light bronchoscopy (WLB), or between their combination (AFB+WLB) and WLB. In these studies, biopsy specimens should contain inflammatory changes, dysplasia and cancer, confirmed by histopathology. Sensitivity, specificity and the area under receiver-operating characteristic curve (AUC) was pooled by a random-effect meta-analysis.

Results: We included seven studies (6 AFB vs. WLB, 1 AFB+WLB vs. WLB) with a total of 343 patients and 808 biopsy specimens. For diagnosing dysplasia and cancer, the median false-positive rate of AFB and WLB was 72% and 59%, respectively. For diagnosing inflammatory changes only, AFB and WLB presented 0.63 (95%CI 0.38 - 0.82) and 0.27 (0.11 - 0.51) sensitivity (P = 0.042), 0.65 (0.30 - 0.89) and 0.80 (0.61 - 0.91) specificity (P = 0.663), and 0.68 (0.64 - 0.72) and 0.59 (0.55 - 0.63) AUC (P = 0.002) respectively. For diagnosing all non-normal lesions (inflammatory changes, dysplasia and cancer), significantly higher sensitivity and AUC was found in AFB as well. Compared with WLB, AFB+WLB also presented higher sensitivity but lower specificity for inflammatory changes only, dysplasia and cancer, or all non-normal lesions.

Conclusions: AFB has potentiality to cover all airway non-normal lesions including inflammatory changes, dysplasia and cancer. Its property of detecting inflammatory changes accounts for the high false-positive detection when diagnosing dysplasia and cancer.

Keywords: *Autofluorescence Bronchoscopy; Non-Normal Lesions; Inflammatory Changes; Lung Cancer*

Introduction

Lung cancer is the leading cause of cancer mortality around the world [1]. In the past several decades, traditional white light bronchoscopy (WLB) has played an important role in the process of diagnosing not only lung cancer, but also other airway non-normal lesions, such as inflammatory changes and dysplasia. In addition, bronchoscopic techniques have developed and become useful tools for lung cancer detection even in the early stage, such as autofluorescence bronchoscopy (AFB) and the combination of AFB and WLB (AFB+WLB).

According to meta-analyses, AFB and AFB+WLB have superior overall diagnostic accuracy to WLB alone for early-stage lung cancer, especially the pre-invasive lesions including dysplasia and carcinoma in situ, which are not easily detected by WLB [2-4]. However, these studies also present the high sensitivity and undesirable specificity of AFB and AFB+WLB. This property could lead to a false-positive detection for early-stage lung cancer, indicating its possible capacity to cover other non-normal lesions rather than dysplasia and cancer, such as inflammatory changes.

To further understanding the false-positive detection of AFB and AFB+WLB when detecting early-stage lung cancer, we conducted this systematic review and meta-analysis to investigate whether their diagnostic capacity could cover non-normal lesions in the airway, including inflammatory changes, dysplasia and cancer.

Methods

Study Searching, Selection, Quality Assessment

We conducted this research based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5]. We searched Web of Science and PubMed according to the inception date of these databases to 31 December 2017. The retrieval formula was: ((Fluorescence OR Autofluorescence OR Auto-fluorescence OR Autofluorescence Imaging) AND Bronchoscopy) AND Cancer [English] [Human].

Studies which investigated AFB and AFB+WLB for diagnosing lung cancer and precancerous lesions were eligible, and 2 × 2 data based on the pathological diagnostic criteria from inflammatory changes (inflammation, hyperplasia, metaplasia), mild/moderate/several dysplasia and cancer (carcinoma in situ, invasive carcinoma) should be calculated. In addition, the eligible studies should directly compare the diagnostic performance between AFB/AFB+WLB and WLB. Duplicated articles were deleted, and articles with inappropriate publication types were excluded, such as reviews, systematic reviews, meta-analyses, case reports, letters, comments. According to the above study inclusion and exclusion criteria, we also searched eligible studies from the database of our previously study [4].

All included studies were assessed based on the tool of Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) [6]. Question 3 in domain 4 "Were all patients included in the analysis?" was replaced by "Were all patients/biopsy specimens included in the analysis?" since the type of calculation for constructing 2 × 2 tables was either a patients-based analysis or a biopsy-based analysis. The risk of bias and concern regarding applicability were scored as "high", "low" and "unclear" according to the answers of questions. Based on these scores in each domain of the tool, we rated the quality for each study (high quality: "low risk" and "low concern" in all domains; low quality: at least one "high risk" or "high concern"; moderate quality: at least one "unclear risk" or "unclear concern", without "high risk" or "high concern").

Data Extraction and Statistical Analysis

We extracted the information of characteristics in each study, including author, year, study site, technique category, number of patients and biopsy specimens. The number of patients and biopsy specimens were only responsible for the final statistical analysis of each individual study; for instance, the number of patients enrolled in studies would not always be the same as the number of patients who were finally analyzed.

According to the diagnostic results of bronchoscopies and histopathology in our included studies, we calculated the false-positive rate of techniques when the detected lesions of lung dysplasia and cancer were considered as the positive results of pathological criteria. For meta-analysis, we extracted the true positive, false positive, false negative and true negative for 2 × 2 tables of included studies; if the articles did not directly provide with these data, we followed corresponding formula to calculate them according to the given sensitivity, specificity, positive/negative predictive value and the number of the pathological lesions in articles [7]. With 2 × 2 data, a bivariate random-effect model was used to estimate pooled sensitivity, specificity, diagnostic odds ratio (DOR) and the area under the summary receiver operating characteristic curve (AUC), based on different detected lesions as the positive results of pathological criteria (all non-normal lesions, dysplasia and cancer, inflammatory changes only). We also plotted the hierarchical summary receiver-operating characteristic (HSROC) curve for the overall performance of these techniques.

The test of heterogeneity with the value of I^2 in meta-analyses lacks sufficient reliability, due to the correlation between sensitivity and specificity (the variation of sensitivity would be mutually influenced by the variation of specificity) [8]. We assumed the heterogeneity existed in our data pooling, and tried to attenuate its effect by using the random-effect model. Moreover, we used meta-regression to estimate the sources of heterogeneity, including the effects of study quality (based on the result of QUADAS-2), the study site and the category of AFB. All pooling procedures and meta-regression were conducted in STATA 13.0 (StataCorp, College Station, TX). For a direct comparison between AFB/AFB+WLB and WLB with the pooled data, we assessed significant difference (if $P < 0.05$) based on the Z test. This procedure was conducted in Excel 2011 (Microsoft, Seattle, Wash).

Result

Study identification, characteristics and quality assessment

The detail of study searching and selection is showed in the flow chart (Figure 1). Seven studies involving 343 patients and 808 biopsy specimens were eligible: six studies of the AFB versus WLB (with 309 patients and 666 biopsy specimens) were included in the meta-analysis [9-14]; one study article investigated AFB+WLB versus WLB (34 patients and 142 biopsy specimens) [15]. There was no low-quality study based on the tool of QUADAS-2. Study characteristics are summarized in table 1 and the detailed diagnostic results of bronchoscopies and histopathology are shown in table 2. The detailed result of quality assessment is demonstrated in table 3.

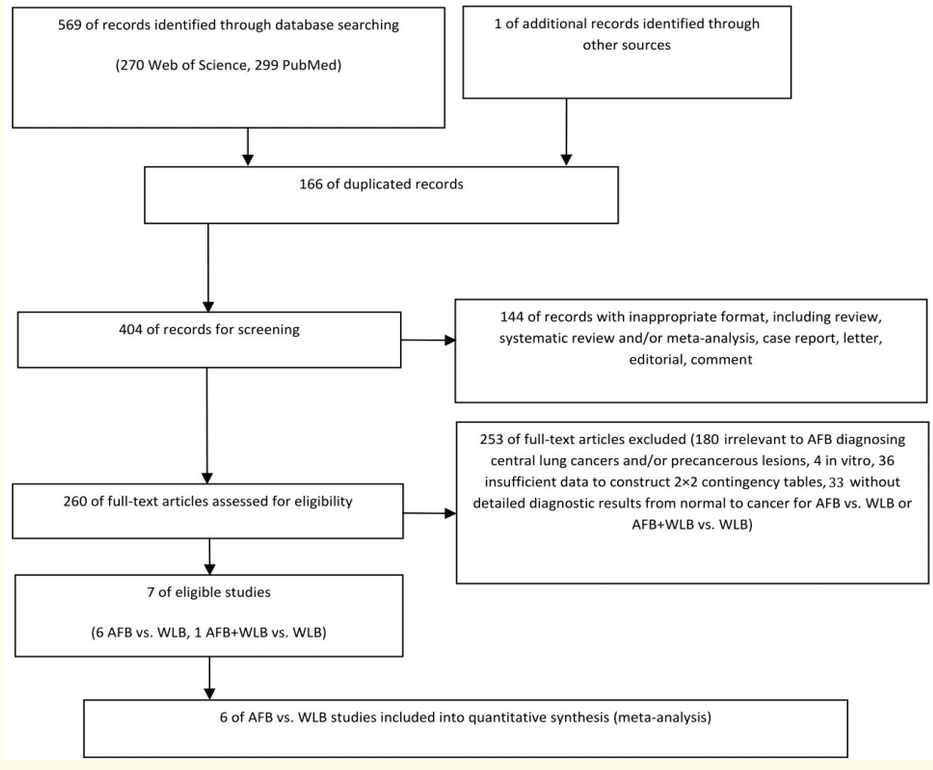

Figure 1: *Study flow chart based on the PRSIMA guideline.*
AFB: Autofluorescence Bronchoscopy; WLB: White Light Bronchoscopy; AFB+WLB: Autofluorescence Bronchoscopy Combined with White Light Bronchoscopy

Author and Year	Study Site	Technique	AFB Category	Patient (n)*	Histopathology Result (n)						Study Quality	False-positive Rate	
					Total	NOR	Other	INF	DYS	CAN		ADV	WLB
Yokomise H 1997	Japan	AFB	LIFE	30	51	24	0	7	4	16	Moderate	31%	41%
Weigel TL 2000	US	AFB	LIFE	25	71	20	0	42	8	1	Moderate	89%	50%
Means-Markwell M 2003	US	AFB	LIFE	28	70	56	0	11	2	1	Moderate	92%	86%
Chhajed PN 2005	Japan	AFB	LIFE	151	343	46	0	166	108	23	High	56%	51%
Lam B 2006	HK	AFB	SAFE1000	62	84	49	1	12	19	3	Moderate	70%	72%
Ali AH 2011	Japan	AFB	SAFE3000	13	47	12	8	18	2	7	High	73%	67%
Vermylen P 1999	Belgium	AFB+WLB	LIFE+WLB	34	142	61	60		15	6	Moderate	83%	76%

Table 1: *Characteristics of included studies.*

**The number of patients are only responsible for the final statistical analysis of each study.*

US: The United States; HK: Hong Kong; NOR: Normal lesions; Other: Other benign lesions; INF: Inflammatory changes, including inflammation, hyperplasia and metaplasia; DYS: Dysplasia, including mild, moderate and severe dysplasia; CAN: Cancer, including carcinoma in situ, invasive carcinoma; False-positive Rate: False-positive rate for diagnosing lung cancer and dysplasia; ADV: Advanced bronchoscopies (AFB or AFB+WLB)

Author and Year	Technique	Histopathology Result (n)										
		Total*	NOR	Other	IMF	HYP	MET	MIL	MOD	SEV	CIS	INV
Yokomise H 1997	AFB vs WLB	51	24	0	0	7	0	4			16	
	AFB +	26	4	0	0	4	0	2			16	
	AFB -	25	20	0	0	3	0	2			0	
	WLB +	22	4	0	0	5	0	1			12	
	WLB -	29	20	0	0	2	0	3			4	
Weigel TL 2000	AFB vs WLB	71	20	0	28	14		5	3		0	1
	AFB +	36	12	0	11	9		1	2		0	1
	AFB -	35	8	0	17	5		4	1		0	0
	WLB +	4	1	0	1	0		1	0		0	1
	WLB -	67	19	0	27	14		4	3		0	0
Means-Markwell M 2003	AFB vs WLB	70	56	0	0	0	11	1	1	0	1	0
	AFB +	36	27	0	0	0	6	1	1	0	1	0
	AFB -	34	29	0	0	0	5	0	0	0	0	0
	WLB +	7	5	0	0	0	1	0	0	0	1	0
	WLB -	63	51	0	0	0	10	1	1	0	0	0
Chhajed PN 2005	AFB vs WLB	343	46	0	125	26	15	48	52	8	3	20
	AFB +	274	37	0	84	21	12	40	49	8	3	20
	AFB -	69	9	0	41	5	3	8	3	0	0	0
	WLB +	181	17	0	53	15	8	28	30	7	3	20
	WLB -	162	29	0	72	11	7	20	22	1	0	0
Lam B 2006	AFB vs WLB	84	49	1	0	0	12	10	5	4	2	1
	AFB +	64	35	1	0	0	9	8	4	4	2	1
	AFB -	20	14	0	0	0	3	2	1	0	0	0
	WLB +	43	24	1	0	0	6	5	3	1	2	1
	WLB -	41	25	0	0	0	6	5	2	3	0	0
Ali AH 2011	AFB vs WLB	47	12	8	2	12	4	2			7	
	AFB +	33	0	8	2	10	4	2			7	
	AFB -	14	12	0	0	2	0	0			0	
	WLB +	18	3	2	1	3	3	2			4	
	WLB -	29	9	6	1	9	1	0			3	
Vermylen P 1999	AFB+WLB vs WLB	142	61	19		9	32	5	10		6	0
	AFB+WLB +	115	41	16		9	29	5	9		6	0
	AFB+WLB -	27	20	3		0	3	0	1		0	0
	WLB +	21	7	3		0	6	1	1		3	0
	WLB -	121	54	16		9	26	4	9		3	0

Table 2: *Diagnostic results of bronchoscopies and histopathology.*

**The data we extracted would be only responsible for the final statistical analysis of each individual study.*

+: Bronchoscopic positive; -: Bronchoscopic negative; HYP: Hyperplasia; MET: Metaplasia; MIL: Mild dysplasia; MOD: Moderate dysplasia; SEV: Severe dysplasia; CIS: Carcinoma in situ; INV: Invasive Carcinoma

Author and Year	Risk of Bias*														Applicability‡ Concerns		
	D1Q1	D1Q2	D1Q3	D1	D2Q1	D2Q2	D2	D3Q1	D3Q2	D3	D4Q1	D4Q2	D4Q3	D4	D1	D2	D3
Yokomise H 1997	U	Y	U	U	Y	Y	L	Y	Y	L	U	Y	Y	L	L	L	L
Weigel TL 2000	U	Y	U	U	Y	Y	L	Y	U	L	U	Y	Y	L	U	L	L
Means-Markwell M 2003	U	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	N	U	L	L	L
Chhajed PN 2005	Y	Y	Y	L	Y	Y	L	Y	U	L	U	Y	Y	L	L	L	L
Lam B 2006	Y	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	N	U	L	L	L
Ali AH 2011	U	Y	Y	L	Y	Y	L	Y	U	L	U	Y	Y	L	L	L	L
Vermylen P 1999	Y	Y	Y	L	Y	Y	L	Y	Y	L	U	Y	N	U	L	L	L

Table 3: *Quality assessment of diagnostic accuracy studies-2 (QUADAS-2).*

**Risk of bias: D1: Domain 1, patient selection; D2: Domain 2, index test; D3: Domain 3, reference standard; D4: Domain 4, flow and timing; D1Q1: Was a consecutive or random sample of patients enrolled? D1Q2: Was a case-control design avoided? D1Q3: Did the study avoid inappropriate exclusions? D2Q1: Were the index test results interpreted without knowledge of the results of the reference standard? D2Q2: If a threshold was used, was it prespecified? D3Q1: Is the reference standard likely to correctly classify the target condition? D3Q2: Were the reference standard results interpreted without knowledge of the results of the index test? D4Q1: Was there an appropriate interval between the index test and reference standard? D4Q2: Did all patients receive the same reference standard? D4Q3: Were all patients/biopsy specimens included in the analysis?*

‡Applicability concern: D1: Domain 1, are there concerns that the included patients and setting do not match the review question? D2: Domain 2, are there concerns that the index test, its conduct, or its interpretation differ from the review question? D3: Domain 3, are there concerns that the target condition as defined by the reference standard does not match the question? Y: Yes; N: No; U: Unclear; H: High; L: Low

Data calculation and meta-analysis

When dysplasia and cancer were considered as the positive result of the pathological criteria, the median false-positive rate of AFB and WLB in the six included studies was 72% and 59%, respectively, and the false-positive rate of AFB+WLB was 83%.

We plotted the HSROC curves for the overall diagnostic performance of the AFB and WLB (Figure 2), and the details of the performance are summarized in table 4. Compared with WLB, regardless of which pathological types of detected lesions were considered as the positive result of the pathological criteria, AFB presented higher pooled sensitivity, AUC, and DOR but lower specificity. When all non-normal lesions or inflammatory changes only were considered as in the positive criteria, the AUC of AFB was significantly higher ($P < 0.001$; $P = 0.002$) than the AUC of WLB; the specificity of AFB was lower, but no significant difference was indicated in this direct comparison.

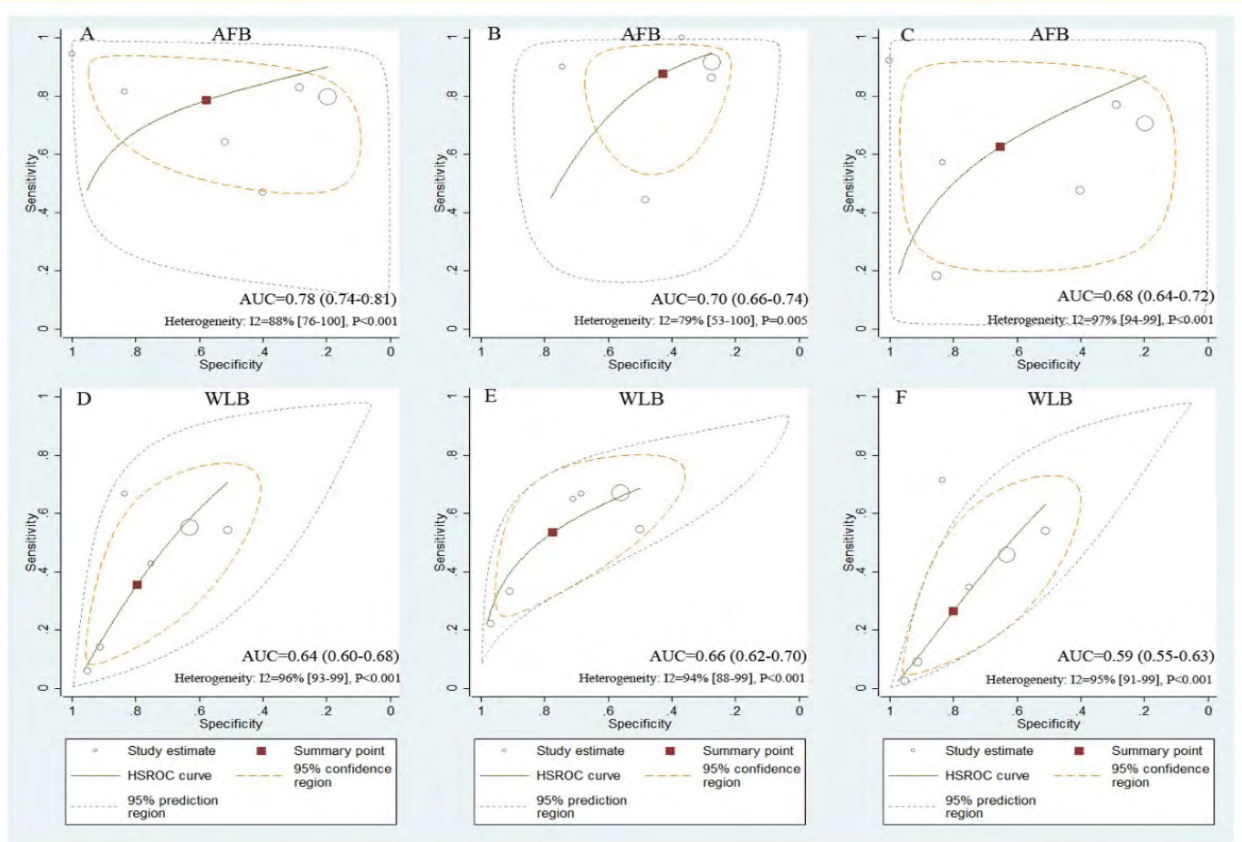

Figure 2: *Hierarchical summary receiver-operating characteristic (HSROC) curve.*

The square in represents the summary point. Circles represent individual studies in meta-analysis. The size of each study is indicated by the size of the circle. The hierarchical summary receiver operating characteristic curves summarize the overall diagnostic accuracy. The dotted line in red color represents 95% confidence region and the dotted line in black color represents 95% prediction region. A, B, C: Overall diagnostic performance of AFB for all non-normal lesions (inflammatory changes, dysplasia and cancer), dysplasia and cancer, inflammatory changes only; D, E, F: Overall diagnostic performance of WLB for all non-normal lesions, dysplasia and cancer, inflammatory changes only.

Pathology Criteria	Technique	Sensitivity*	P	Specificity*	P	AUC*	P	DOR*	P
All Non - normal Lesions‡	AFB	0.79 (0.63 - 0.89)	0.003	0.58 (0.26 - 0.84)	0.181	0.78 (0.74 - 0.81)	< 0.001	5 (1 - 32)	0.188
	WLB	0.35 (0.17 - 0.59)		0.80 (0.61 - 0.91)		0.64 (0.60 - 0.68)		2 (1 - 4)	
Dysplasia§ and Cancer¶	AFB	0.88 (0.73 - 0.95)	0.002	0.43 (0.30 - 0.56)	0.005	0.70 (0.66 - 0.74)	0.05	5 (2 - 15)	0.188
	WLB	0.54 (0.37 - 0.69)		0.77 (0.57 - 0.90)		0.66 (0.62 - 0.70)		4 (2 - 8)	
Inflammatory Changes*	AFB	0.63 (0.38 - 0.82)	0.042	0.65 (0.30 - 0.89)	0.663	0.68 (0.64 - 0.72)	0.002	3 (1 - 20)	0.165
	WLB	0.27 (0.11 - 0.51)		0.80 (0.61 - 0.91)		0.59 (0.55 - 0.63)		1 (1 - 3)	

Table 4: *Diagnostic performance of AFB versus WLB based on 6 comparative studies with 309 patients and 666 biopsy specimens.*
**Data in parentheses are 95% CIs*
‡All non-normal lesions = Inflammatory Changes, Dysplasia and Cancer
§Dysplasia including mild/moderate/severe dysplasia
¶Cancer including carcinoma in situ and invasive carcinoma
**Inflammatory changes indicating inflammation, hyperplasia or metaplasia*
P: P value for direct comparison; AUC: Area Under the summary receiver operating characteristic Curve; DOR: Diagnostic Odds Ratio

Instead of the study quality and the category of AFB, meta-regression indicated the study site could be the source of heterogeneity during our data synthesis (Table 5).

Source of Heterogeneity	Tech	All Non - normal Lesions		Dysplasia and Cancer		Inflammatory Changes	
		I^2 (%)	P (Joint)*	I^2 (%)	P (Joint)*	I^2 (%)	P (Joint)*
Study Quality: High vs Moderate	AFB	36 (0 - 100)	0.21	52 (0 - 100)	0.12	40 (0 - 100)	0.19
	WLB	0 (0 - 100)	0.64	8 (0 - 100)	0.34	0 (0 - 100)	0.62
Study Site: Asia vs Non - Asia	AFB	83 (63 - 100)	< 0.01	70 (33 - 100)	0.04	69 (30 - 100)	0.04
	WLB	89 (78 - 100)	< 0.01	87 (74 - 100)	< 0.01	87 (72 - 100)	< 0.01
System: LIFE vs SAFE	AFB	36 (0 - 100)	0.21	5 (0 - 100)	0.35	62 (15 - 100)	0.07
	WLB	42 (0 - 100)	0.18	23 (0 - 100)	0.27	18 (0 - 100)	0.29

Table 5: *Meta-regression for the source of heterogeneity.*
**P (Joint) is the P value for the sources of heterogeneity, considering sensitivity and specificity together.*

Compared with WLB, AFB+WLB had higher sensitivity but lower specificity regardless of different pathological diagnostic criteria (Table 6).

Pathology Criteria	Technique	Sensitivity	Specificity
All Non-normal Lesions	AFB+WLB	0.91	0.33
	WLB	0.17	0.89
Dysplasia and Cancer	AFB+WLB	0.95	0.21
	WLB	0.24	0.87
Inflammatory Changes	AFB+WLB	0.90	0.33
	WLB	0.18	0.87

Table 6: *Diagnostic performance of AFB+WLB versus WLB based on one study.*

Discussion

To our knowledge, it is the first systematic review and meta-analysis to investigate the diagnostic accuracy between advanced bronchoscopic techniques (AFB, AFB+WLB) and conventional white light bronchoscopy (WLB) for non-normal lesions in the airway, including inflammatory changes, dysplasia and cancer. Our results suggested that AFB not only has the detective capacity for dysplasia and lung cancer, but also can detect inflammatory changes.

Even though the relatively poor resolution of the visual field would limit the broader application of AFB, we still find this technique presents a superior diagnostic performance compared to WLB for airway lesions ranging from inflammation to invasive carcinoma. This finding may be explained by its remarkable sensitivity to mucosal non-normal lesions with hyperemia or the enrichment of the blood vessels (one of the shared manifestations of inflammatory changes and early lung cancer). Accordingly, our findings indicated that we could make a broader use of this technique in our clinical practice for detecting not just early lung cancer but also other diseases with inflammatory changes, particularly in the diseases that would not be easily detected by computed tomography or laboratory examinations.

Based on the property to cover non-normal lesions and the low specificity for early lung cancer, it is easily understood that the false-positive rate was close to 70% in previous studies when AFB was used for diagnosing airway early lung cancer, which means this technique does not have the capacity to distinguish different kind of non-normal lesions in the airway. However, due to the property of its remarkable sensitivity, more biopsy specimens in different sites of the central airway could be taken based on the suggestion from the images of AFB and finally confirmed by histopathology, in order to diminish the possibility of a missed diagnosis for patients with unknown respiratory diseases, especially the early-stage lung cancer.

Development of bronchoscopic techniques is needed for precise diagnosis. The addition of WLB to AFB may be a good strategy to improve the specificity for detecting airway non-normal lesions. However, currently none of our included studies could support this assumption.

Limitation

Some limitations to the present study need to be acknowledged. First, we did not include the studies of techniques only diagnosing inflammatory changes. Instead, we included the studies with the purpose of cancer detection, as we aim to investigate the capacity of the techniques for diagnosing all non-normal lesions, as well as to understand their degree of the false-positive detection when diagnosing lung cancer and precancerous lesions (dysplasia). In addition, as few original studies would specifically focus on such a rather non-specific clinical entity of the airway non-normal lesions, variation in diagnostic criteria and/or threshold cannot be excluded. Third, we set different pathological diagnostic criteria to investigate the performance of bronchoscopic techniques, but this classification does not mean that all techniques can distinguish a pathological degree of detected lesions, or that pathological classification of detected lesions was known before the bronchoscopic procedure in our included studies. In fact, the pathological types of the lesions could only be diagnosed by pathologists after examining the sample taken from the airway. Moreover, during our data synthesis, heterogeneity between different studies existed, and the source of this heterogeneity may be the study site of our included studies. In addition to the study site, we assume the insufficient number of biopsy specimens was the other reason for the heterogeneity, especially the insufficient number of dysplasia and cancer specimens in some of our included studies, which may have had a strong effect on the heterogeneity when sensitivity was being calculated. Given that the nature of our research limits us to consider some factors with respect to the details of study procedure in our included studies for further analysis, the convincingness of our research could be attenuated. For example, there are no uniform diagnostic methods in using AFB based on different categories; we assume the investigators in the included studies have used appropriate criteria for diagnosing the airway lesions based on their situations.

Conclusion

Autofluorescence bronchoscopy has potentiality to cover all airway non-normal lesions including inflammatory changes, dysplasia and cancer, but without the capacity to distinguish these lesions. This property may account for the high false-positive detection when diagnosing early lung cancer.

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Conflict of Interests

The authors declare that they have conflict of interests.

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