The Value of Autofluorescence Bronchoscopy Combined with White Light Bronchoscopy Compared with White Light Alone in the Diagnosis of Intraepithelial Neoplasia and Invasive Lung Cancer

A Meta-Analysis

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Objective: To compare the accuracy of autofluorescence bronchoscopy (AFB) combined with white light bronchoscopy (WLB) versus WLB alone in the diagnosis of lung cancer.

Methods: The Ovid, PubMed, and Google Scholar databases from January 1990 to October 2010 were searched. Two reviewers independently assessed the quality of the trials and extracted data. The relative risk for sensitivity and specificity on a per-lesion basis of AFB + WLB versus WLB alone to detect intraepithelial neoplasia and invasive cancer were pooled by Review Manager.

Results: Twenty-one studies involving 3266 patients were ultimately analyzed. The pool relative sensitivity on a per-lesion basis of AFB + WLB versus WLB alone to detect intraepithelial neoplasia and invasive cancer was 2.04 (95% confidence interval [CI] 1.72–2.42) and 1.15 (95% CI 1.05–1.26), respectively. The pool relative specificity on a per-lesion basis of AFB + WLB versus WLB alone was 0.65 (95% CI 0.59–0.73).

Conclusions: Although the specificity of AFB + WLB is lower than WLB alone, AFB + WLB seems to significantly improve the sensitivity to detect intraepithelial neoplasia. However, this advantage over WLB alone seems much less in detecting invasive lung cancer.

Key Words: Autofluorescence bronchoscopy, White light bronchoscopy, Intraepithelial neoplasia, Invasive lung cancer, Meta-analysis.

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Lung cancer is the leading cause of cancer mortality globally.[1] The Third National inquest case study researched by the Health Ministry of China in 2008 reported that the major incidence of lung cancer increased 465% in the past 30 years in China. Although surgery for early stage lung cancers offers a relatively good prospect of cure, 5-year survival rates for patients with stage IA disease are 73%; however, for those with disease at stages II to IV, the rates range from 46 to 9%.[2] Currently, only 16% of lung cancers are diagnosed when disease is localized, and fewer lung cancers are diagnosed at stage 0, resulting in a combined 5-year survival rate of only 15%.[3] Therefore, more sensitive methods for detecting clinically silent lung cancers at the earlier stages are greatly needed.

White light bronchoscopy (WLB) is a commonly used diagnostic tool for obtaining tissue for the definitive diagnosis of lung cancer. However, WLB is limited in its ability to detect small intraepithelial and microinvasive/preinvasive lesions, which may be only a few cells thick and might only have a surface diameter of a few millimeters. Autofluorescence bronchoscopy (AFB) was developed to address this limitation of WLB.[4] AFB has been shown to be a far more sensitive method of detecting microinvasive/preinvasive lesions. However, the literature gives confusing results regarding the sensitivity and specificity of detecting these lesions when AFB + WLB is compared with WLB alone. For the proper use of fluorescence bronchoscopy for the diagnosis of central-type early lung cancer, we systematically reviewed the literature to summarize the evidence for the value of AFB + WLB versus WLB alone in the diagnosis of microinvasive/preinvasive and invasive lung cancer.

MATERIALS AND METHODS

Search Strategy

We searched for articles comparing the value of AFB + WLB versus WLB alone, using search engines in Ovid, PubMed, and Google Scholar from January 1990 to October 2010. The following key words were used: "AFB" or "fluo-

rescence bronchoscopy" or "autofluorescence endoscopy" or "fluorescence endoscopy," and "WLB" or "conventional bronchoscopy" or "video bronchoscopy." We compared sources to exclude duplicate references (i.e., the same outcomes reported on the same cohort). Reference lists of included studies and review articles were manually searched.

Study Selection

Inclusion criteria were (a) articles were published in English; (b) AFB and WLB were used in the diagnosis of intraepithelial neoplasia and invasive lung cancer; (c) histopathology analysis was used as the reference standard; (d) for per-lesion statistics, sufficient data were presented to calculate the sensitivity and specificity of intraepithelial neoplasia (moderate/severe dysplasia or carcinoma in situ [CIS]) and invasive lung cancer; and (e) when data or subsets of data were presented in more than one article, the article with most details or the most recent article was chosen.

Data Extraction

Information was extracted from all eligible publications, independently by two reviewers (J.S. and J.Y.), according to the inclusion criteria listed earlier. Disagreement was resolved by discussion between the two reviewers. Relevant studies were further examined with Quality Assessment of Diagnostic Accuracy Studies criteria.[5] The following data were collected from each study: first author's surname, year of publication, type of AFB, average subject age, sample size, patient characteristics, and outcome. To compare the diagnostic value for lung cancer of the two types of bronchoscopies, we studied the sensitivity and specificity of the two to diagnose intraepithelial neoplasia and invasive cancer, respectively.

Statistical Analysis

The relative risk (RR) for sensitivity and specificity on a per-lesion basis of AFB + WLB versus WLB alone to detect intraepithelial neoplasia or invasive cancer were calculated by Review Manager (RevMan; version 4.2. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration). A statistical test with a p less than 0.05 was considered significant. RR of more than 1 reflects more sensitivity of in AFB + WLB and vice versa. The results were generated using the fixed-effects model. A random-effect model was employed when there was evidence of significant statistical heterogeneity, generating a more conservative estimate. All p values were two sided. All confidence intervals (CIs) had a two-sided probability coverage of 95%. Subgroup analysis was carried out to look at the diagnostic value of the different types of AFB. An estimate of potential publication bias was carried out using funnel plotting, in which the standard error of log (RR) of each study was plotted against its log (RR). An asymmetric plot suggested a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a well-established linear regression approach to measure the funnel plot asymmetry on the natural logarithm scale of the RR. The significance of the intercept was determined by the t test suggested by Egger ($p < 0.05$ was considered representative of statistically significant publication bias) calculated by using STATA version 10.0 (Stata Corporation, College Station, TX). Linear regression was also calculated by STATA.

RESULTS

Trial Flow

Two hundred seventy-three reports were originally retrieved after electronic searching, and 41 studies were identified after scanning the titles and abstracts. Twenty studies were excluded for the following reasons: (a) only AFB was performed[6–8]; (b) sufficient data not presented to calculate sensitivity and specificity[9–18]; (c) positive result not moderate/severe dysplasia, CIS, or invasive cancer[19–21]; (d) where data presented in more than one article, article with fewest details was excluded[22]; and (e) studies were not per-lesion based[23–25] (Figure 1).

Characteristics of Included Studies

Twenty-one studies meeting the inclusion criteria were identified.[26–46] WLB was performed in all studies, whereas different types of AFB were used in different studies. The light-induced fluorescence endoscopy (LIFE) device (Xillix Technologies; Vancouver, BC, Canada) was used in 12 studies. The Storz D-Light system (D-Light, Karl Storz company, Germany) and Pentax SAFE-1000 systems (Pentax, Tokyo, Japan) were performed in three studies each. The Pentax SAFE-3000 system (Pentax), Onco-LIFE device (Xillix Technologies; Richmond), and PDS-2000 (Hamamatsu Photonics K.K.,Hamamatsu, Japan) were performed in one study each. Among the 21, 19 studies had sufficient data to analyze the RR for sensitivity of WLB + FLB versus WLB alone to detect intraepithelial neoplasia, whereas 14 studies were used to analyze the RR for sensitivity of WLB + FLB versus WLB alone to detect invasive cancer. Sixteen studies were used to analyze the RR for specificity of WLB + AFB versus WLB

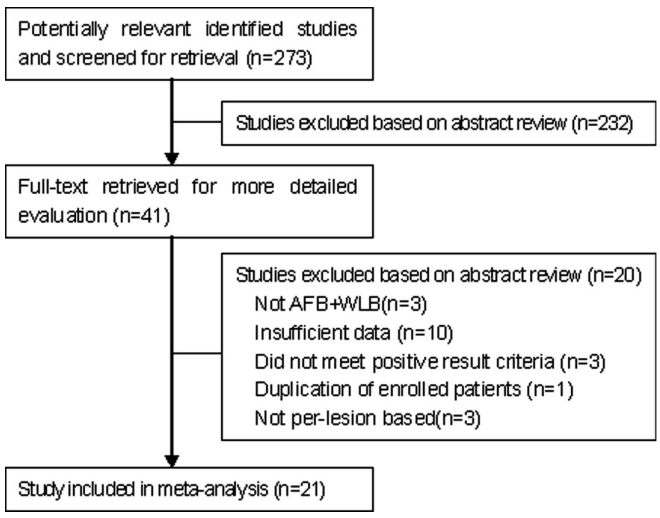

FIGURE 1. Flow of identifying the studies. AFB, autofluorescence bronchoscopy; WLB, white light bronchoscopy.

TABLE 1. Characteristics of Included Studies

Reference	Category of AFB	Average Age (yr)	No. of Subjects	No. of Biopsies	Preinvasive Lesions				Invasive Cancer				Specificity	
							Sensitivity (%)				Sensitivity			
					N	Prevalence (%)	WLB	AFB + WLB	*N*	Prevalence (%)	WLB	AFB + WLB	WLB	AFB + WLB
Edell et al.[27]	Onco-LIFE	62	170	776	41	5.28	9.76	41.46	35	4.51	91.43	100.00	94.00	75.00
Nakanishi et al.[33]	PDS-2000	69	71	288	29	10.07	27.59	75.86	16	5.56	75.00	93.75	77.37	52.67
Jang et al.[35]	D-Light	62	113	283	16	5.65	25.00	93.75			NR		93.33	50.00
Lam et al.[34]	SAFE-1000	60	62	84	11	13.10	54.55	100.00	1	1.19	100.00	100.00	NR	
Ikeda et al.[36]	SAFE-3000	68	154	166	48	28.92	66.67	100.00	30	18.07	100.00	100.00	NR	
Häussinger et al.[38]	D-Light	59	1173	2907	53	1.82	57.89	82.35			NR		62.12	58.38
Chhajed et al.[37]	LIFE	67	151	343	63	18.37	63.49	96.83	20	5.83	100.00	100.00	53.46	17.69
Moro-Sibilot et al.[39]	LIFE	60	244	354	42	11.86	35.71	85.71	39	11.02	74.36	76.92	96.34	82.78
van Rens et al.[42]	LIFE	66	72	88	15	17.05	20.00	100.00	1	1.14	100.00	100.00	NR	
Shibuya et al.[41]	LIFE	68	64	212	45	21.23	68.89	91.11	21	9.91	100.00	100.00	65.75	31.51
Hirsch et al.[40]	LIFE	68	55	391			NR				NR		77.64	29.39
Vermylen et al.[43]	LIFE	59	34	142	16	11.27	25.00	93.75			NR		86.51	20.63
Weigel et al.[26]	LIFE	65	36	89			NR				NR		86.75	48.19
Ikeda et al.[31]	LIFE	64	158	262	84	32.06	58.33	100.00	43	16.41	100.00	100.00	62.22	44.44
Venmans et al.[32]	LIFE	65	95	681	79	11.60	59.49	84.81	21	3.08	100.00	100.00	84.85	60.41
Kakihana et al.[29]	SAFE-1000	NR	72	147	55	37.41	52.73	100.00	24	16.33	100.00	100.00	NR	
Häußinger et al.[28]	D-Light	62	56	264	7	2.65	28.57	71.43	36	13.64	80.56	83.33	93.21	86.43
Horvath et al.[30]	SAFE-1000	51	60	146	5	3.42	0.00	100.00			NR		91.49	76.60
Lam et al.[44]	LIFE	63	173	700	102	14.57	8.82	55.88	40	5.71	65.00	95.00	90.32	65.95
Ikeda et al.[45]	LIFE	NR	30	77	28	36.36	35.71	100.00	13	16.88	92.31	100.00	NR	
Lam et al.[46]	LIFE	NR	223	451	113	25.06	38.94	84.07			NR		91.12	81.36

AFB, autofluorescence bronchoscopy; WLB, white light bronchoscopy; NR, not reported.

alone (Table 1). The size of the cohorts varied from 30 to 1173, with the total number being 3266 patients.

Publication Bias and Heterogeneity

Publication bias was found according to funnel plot in the articles enrolled in the analysis of RR for sensitivity detection of intraepithelial neoplasia (Figure 2; Begg's test, $p = 0.039$; Egger's test, $p = 0.000$). Heterogeneity was both found in sensitivity to detect intraepithelial neoplasia and specificity ($p < 0.05$). Therefore, a random effect model was used for the meta-analysis to obtain a summary estimate for sensitivity and specificity with 95% CI. To explore the possible source of heterogeneity, subgroup analyses were applied. Heterogeneity was also found in the LIFE subgroup.

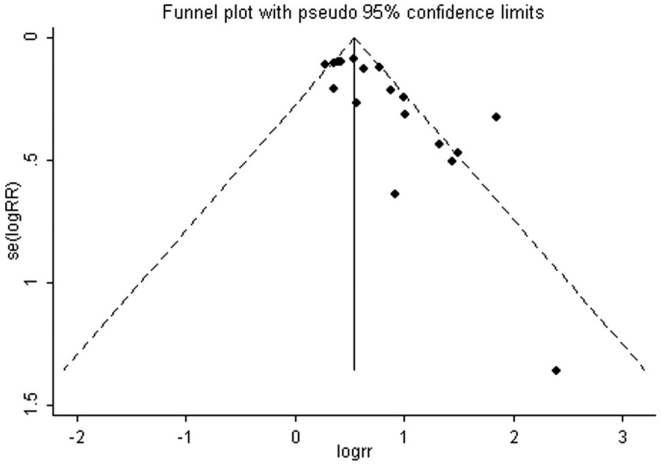

FIGURE 2. Funnel plot of 19 studies included in the analysis of relative risk (RR) for sensitivity of autofluorescence bronchoscopy + white light bronchoscopy (WLB) versus WLB to detect intraepithelial neoplasia.

Relationship between Prevalence and Sensitivity

Linear regression suggested that the sensitivity correlated with the prevalence of intraepithelial neoplasia, both for WLB($r^2 = 0.208$, $p = 0.049$) and AFB + WLB($r^2 = 0.214$, $p = 0.046$), but not correlated with the prevalence of invasive cancer ($r^2 = 0.004$, $p = 0.821$; $r^2 = 0.016$, $p = 0.664$).

Meta-Analysis Results

Relative Sensitivity to Detect Intraepithelial Neoplasia

The pool sensitivity on a per-lesion basis of AFB + WLB and WLB to detect intraepithelial neoplasia was 84.63 and 42.54%, respectively. The pool relative sensitivity of AFB + WLB versus WLB was 2.04 (95% CI 1.72–2.42) and was statistically significant ($p < 0.00001$).[27–39,41–46] Onco-LIFE had the highest RR (4.25; 95% CI, 1.56–11.55), but only one study was included. The analysis in the subgroups whose enrolled studies were more than one showed that the

highest RR was 2.16 in D -Light (95% CI 1.06–4.39). SAFE-1000 was the lowest at 1.88 (95% CI 1.50–2.36), and the LIFE RR was 2.10 (95% CI 1.66–2.66). The RR of the other subgroups was as follows: SAFE-3000, 1.49 (95% CI 1.22–1.83) and PDS-2000, 2.75 (95% CI 1.47–5.13). The test of heterogeneity for the 19 studies was significant ($p < 0.00001$). Thus, RR was calculated using a random-effect model (Figure 3).

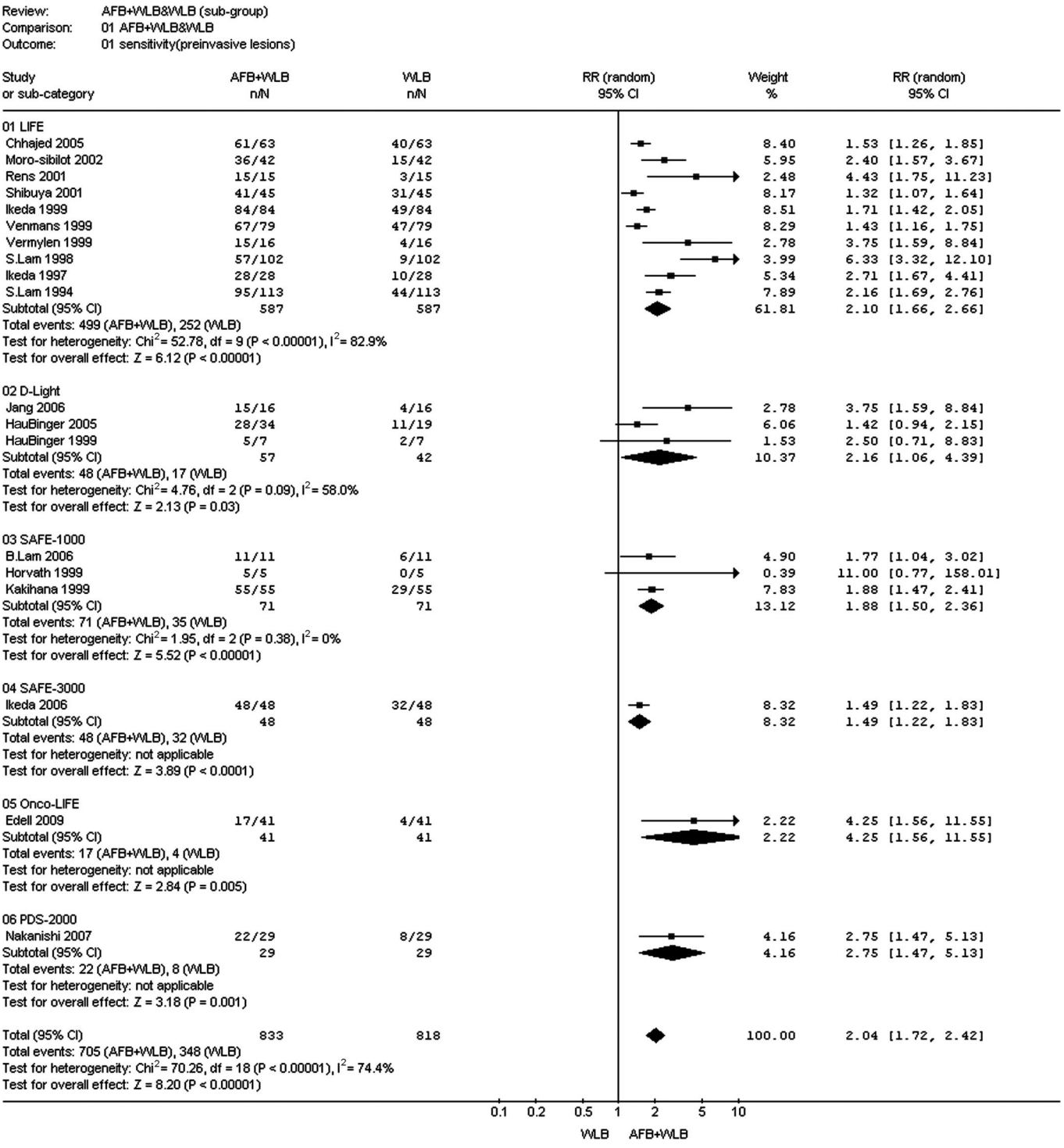

FIGURE 3. Forest plot of relative risk for subgroup and overall sensitivity of autofluorescence bronchoscopy (AFB) + white light bronchoscopy (WLB) versus WLB to detect intraepithelial neoplasia. CI, confidence interval.

Relative Sensitivity to Detect Invasive Cancer

The pool sensitivity on a per-lesion basis of AFB + WLB versus WLB to detect invasive cancer was 94.71 and 88.53%, respectively. The pool relative sensitivity of AFB + WLB versus WLB was 1.15 (95% CI 1.05–1.26) and was statistically significant ($p = 0.003$).[27–29,31–34,36,37,39,41,42,44,45] Only the RR of LIFE was statistically significant ($p = 0.01$), with a value of 1.21 (95% CI 1.04–1.40) among the subgroups. The RR of other subgroups was not statistically significant ($p > 0.05$). PDS-2000 had the highest RR (1.25, 95% CI 0.92–1.70), but only one study was enrolled. The RR of the other subgroups was as follows: D-Light, 1.03 (95% CI 0.83–1.29) and Onco-LIFE, 1.09 (95% CI 0.97–1.22). The RR of both SAFE-1000 and SAFE-3000 were 1. The test of heterogeneity for the 14 studies was not significant ($p = 0.23$). Thus, the RR was calculated using a fixed-effect model (Figure 4).

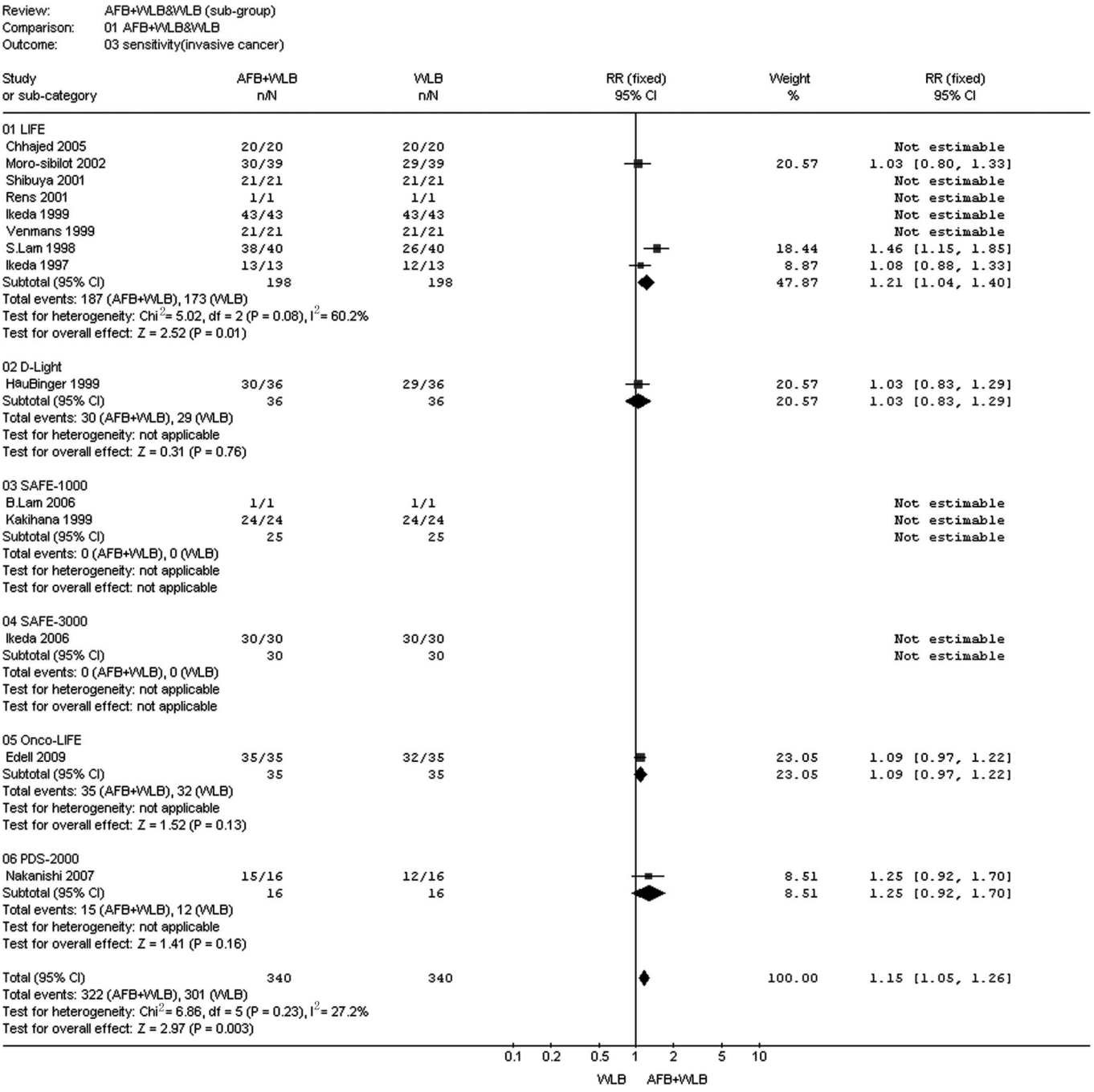

FIGURE 4. Forest plot of relative risk (RR) for subgroup and overall sensitivity of autofluorescence bronchoscopy (AFB) + white light bronchoscopy (WLB) versus WLB to detect invasive cancer. CI, confidence interval.

Relative Specificity

The pool specificity on a per-lesion basis of AFB + WLB versus WLB was 60.94 and 79.70%, respectively. The pool relative specificity on a per-lesion basis of AFB + WLB versus WLB was 0.65 (95% CI 0.59–0.73) and was statistically significant ($p < 0.00001$).[26–28,30–33,35,37–41,43,44,46] The RR of the subgroups were as follows: LIFE, 0.56 (95% CI 0.47–0.68); D-Light, 0.78 (95% CI 0.62–0.99); SAFE-1000, 0.84 (95% CI 0.75–0.93); Onco-LIFE, 0.80 (95% CI 0.76–0.84); and PDS-2000, 0.68 (95% CI 0.59–0.78). The test of heterogeneity for the 16 studies was significant ($p < 0.00001$). Thus, the RR was calculated using a random-effect model (Figure 5).

Adverse Effects

Adverse effects were reported in two studies. In one study,[27] reported adverse effects were seen in nine patients. All adverse effects were commensurate with bronchoscopy, with none being attributable to the AFB devices. Serious complications include fever and hypoxia, resulting in hospitalization in four patients. Ikeda et al.[36] reported only minor adverse effects such as faint blood-tinged sputum and mild

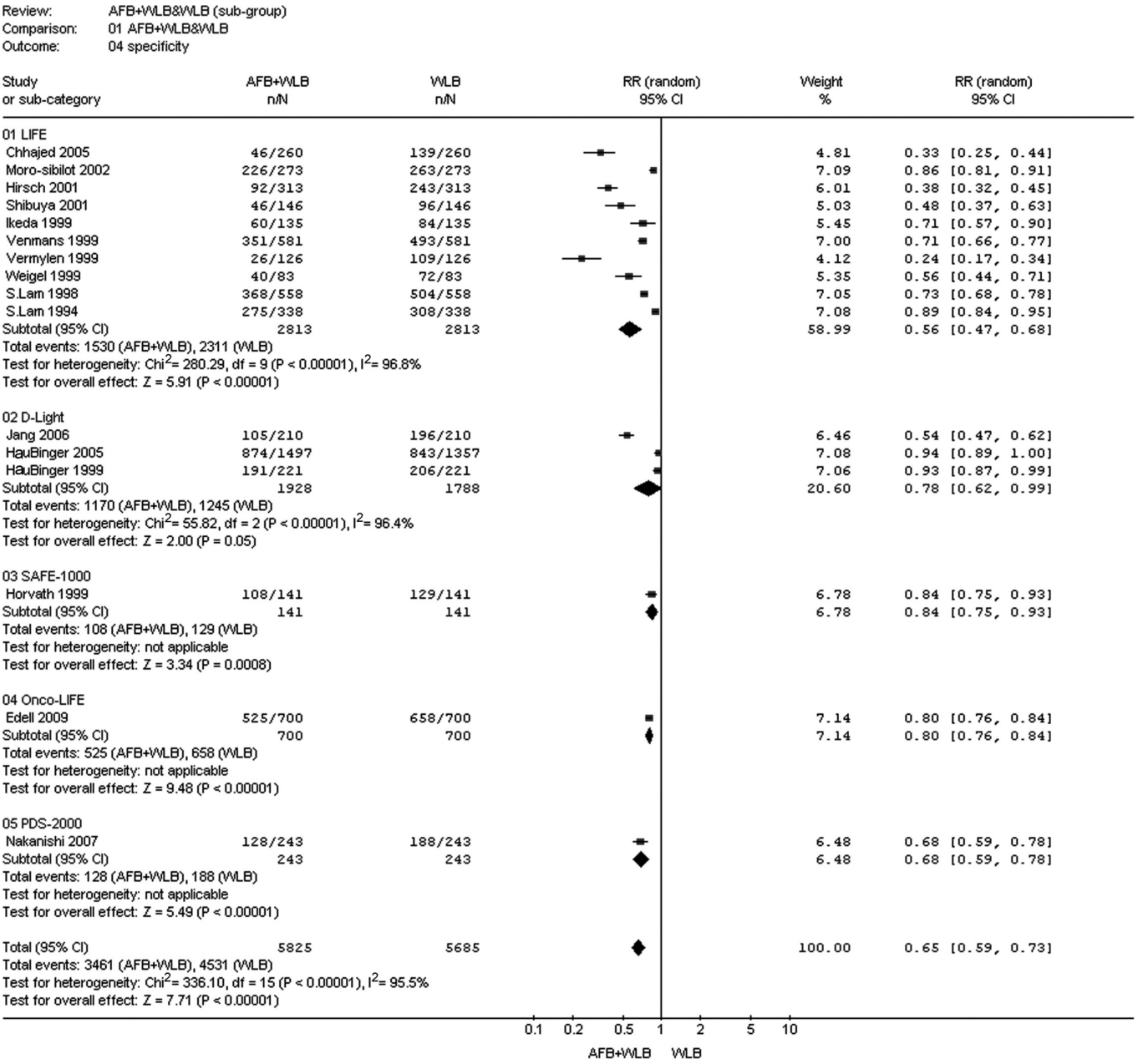

FIGURE 5. Forest plot of relative risk (RR) for subgroup and overall specificity of autofluorescence bronchoscopy (AFB) + white light bronchoscopy (WLB) versus WLB. CI, confidence interval.

cough, commonly associated with routine bronchoscopic examination, with there being no specific relation to the AFB examination.

DISCUSSION

Detection of cancers at an early stage, followed by complete surgical resection, is the only curative treatment approach currently available for the majority of lung cancer patients. Advances in bronchoscopy[47] and the use of sputum cytology have helped to increase the detection of central-type early lung cancer. WLB is usually used in the detection of lung cancer. Nevertheless, although this type of bronchoscopy can detect early lung cancer, the detection of preinvasive lesions is difficult even for experienced bronchoscopists. One study[48] showed that only 29% of CIS lesions were visible to experienced bronchoscopists using WLB.

According to our meta-analysis, AFB + WLB can effectively and significantly improve the sensitivity to detect only intraepithelial neoplasia compared with WLB alone, the pool relative sensitivity of AFB + WLB versus WLB to detect intraepithelial neoplasia is 2.04. It has been reported in Bronchial Intraepithelial Neoplasia/Early Central Airways Lung Cancer, ACCP Evidence-Based Clinical Practice Guidelines (2nd edition) that the pool sensitivity on a per-lesion basis of AFB + WLB and WLB to detect intraepithelial neoplasia was 80 and 40%, respectively; the pool specificity was 60 and 81%, respectively; and the pool relative sensitivity of AFB + WLB versus WLB was 2.[49] Although the literatures enrolled in our meta-analysis were 38.9% same to this guideline for the different enrollment standard and the results of the guideline were not obtained by meta-analysis, our conclusions were surprisingly similar. Thus, we believe that our results are credible.

Although the sensitivity of AFB combined with WLB to detect invasive cancer was improved, its RR was only 1.15, which is much lower than the RR for sensitivity to detect intraepithelial neoplasia. If one is screening for invasive cancer, then, perhaps only WLB is needed. It is less expensive, easier to perform, and can be done in more centers and used more widely in populations whose chest radiology evidences are suspicious of central airways lesion. Thus, using WLB alone would seem to be cost effective.

The disadvantage of AFB is the lower specificity compared with WLB. The specificities of AFB + WLB in this meta-analysis were all decreased, compared with WLB alone, and the specificity of AFB + WLB was only 65% of WLB alone. The reason for the low specificity is that AFB has difficulty in distinguishing between preinvasive lesions and other benign epithelial changes such as bronchitis, which is frequently present in patients whose sputum cytology is suspicious or positive for malignancy.[41] Some anthropic factors, such as severe coughing during AFB examination or AFB, were performed in patients after brushing or biopsy by recent WLB; all can result in false positive. The low specificity of AFB is also problematic because more biopsies are needed, resulting in greater cost and potential patient harm.

Bronchoscopic devices subsequent to LIFE have made many improvements. SAFE 1000 system uses a xenon lamp, instead of the laser used in the LIFE system. A new version (SAFE-3000), incorporating single action image switching and simultaneous display, is now available. Storz D-light and Onco-LIFE systems combine autofluorescence and reflected light. AFI (Olympus Medical System Corp., Tokyo, Japan) has developed a display of a composite image, integrating three signals: an autofluorescence signal plus reflected green (G) and red (R) light signals. AFI will display a light green image for normal epithelium and blue or magenta for an abnormal fluorescence, depending on the condition of abnormal epithelium. This may be more objective than the LIFE system, under which normal areas appear as green, whereas areas suspicious for moderate dysplasia or greater have a definite brown or brownish-red color. In one study, the AFI system had better sensitivity (80%) and specificity (83%) than the LIFE system.[8] Also, some studies reported that AFI has a higher sensitivity and specificity than WLB.[7,17] However, these studies were not enrolled in our analysis because they did not match our inclusion criteria. In addition to equipment upgrades, quantitative methods have also been reported to improve the sensitivity and specificity for diagnosing lung cancer. One study reported about AFB (PDS-2000) images that were analyzed using Photoshop 6.0 (Adobe Systems Inc., San Jose, CA). Normal and abnormal bronchial parts were defined. Color histograms for red, green, and blue were generated in each area, using a histogram tool. Then the R:G ratio was calculated.[33]

Our findings are limited because of data heterogeneity. Possible reasons are as follows: (1) studies enrolled in the meta-analysis were over a long time span 1994 to 2009; (2) use of different types of AFB, but mainly LIFE (57.14%); studies of other types of AFB were few or not match our enrollment standard; (3) study populations were different in many articles, with some having patients with known or suspected lung cancer, whereas others had patients only with high risk of lung cancer, resulting in different prevalence of lesions. Linear regression suggested that the sensitivity correlated with the prevalence of intraepithelial neoplasia, both for WLB and AFB + WLB. Therefore, an important issue is to define a population recommended for AFB examination. Thoracic computed tomography is a sensitive method for detecting early lung cancer but has a high false-positive rate and is not as sensitive for detecting central preinvasive and microinvasive cancers. Conventional sputum cytology is hampered by a low sensitivity, but this can be improved by using DNA analyses of sputum slides, using automated sputum cytology, but with a modest reduction of specificity.[50–53] Thus, patients with positive automated sputum cytology, but with chest imaging studies showing no localizing abnormality, may be a defined population recommended for having an AFB examination for detection of early lung cancer. The efficiency of AFB in detecting early lung cancer may thereby be enhanced in the setting of such dual screening.

In conclusion, compared with application of WLB alone, AFB + WLB seems to significantly improve the sensitivity and ability to detect intraepithelial neoplasia. However, this advantage over WLB alone seems much less in detecting invasive lung cancer. Although the specificity of

AFB is lower than WLB, the development of newer instruments of AFB and the application of quantitation methods might improve the specificity of AFB, which would shorten examination time, reduce biopsy site size, and decrease risk and cost.

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