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Review

Diagnostic Value of Autoantibodies in Lung Cancer: a Systematic Review and Meta-Analysis

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Key Words
Lung cancer • Tumor-associated autoantibodies • Diagnosis • Meta-analysis

Abstract
Background/Aims: Recently, many studies have demonstrated that various tumor-associated autoantibodies have been detected in early stages of lung cancer. Therefore, we conducted a meta-analysis to comprehensively evaluate available evidence on the diagnostic value of autoantibodies against tumor-associated antigens in lung cancer. ***Methods:*** We systematically searched PubMed, Scopus, Web of Science and other databases through 23 March 2018. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2. We used the bivariate mixed-effect models to calculate pooled values of sensitivity, specificity, positive likelihood ratios, negative likelihood ratios, diagnostic odds ratios and associated 95% confidence intervals. Summary receiver operating characteristic (SROC) curves were used to summarize overall test performance. Deek's funnel plot was used to detect publication bias. ***Results:*** Review of 468 candidate articles identified fifty-three articles with a total of 11,515 patients for qualitative review and meta-analysis. Pooled sensitivity, specificity and area under the SROC curve were as follows for tumor-associated autoantibodies against the following proteins: p53, 0.19, 0.98, 0.82; NY-ESO-1, 0.17, 0.98, 0.90; Survivin, 0.19, 0.99, 0.96; c-myc, 0.14, 0.98, 0.45; Cyclin B1, 0.18, 0.98, 0.91; GBU4-5, 0.07, 0.98, 0.91; CAGE, 0.14, 0.98, 0.90; p16, 0.08, 0.97, 0.91; SOX2, 0.14, 0.99, 0.93; and HuD, 0.17, 0.99, 0.82. ***Conclusion:*** Each tumor-associated autoantibody on its own showed excellent diagnostic specificity for lung cancer but inadequate sensitivity. Our results suggest that combinations or panels of tumor-associated autoantibodies may provide better sensitivity for diagnosing lung cancer, and the diagnostic accuracy of tumor-associated autoantibodies should be validated in more studies.

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Introduction

Lung cancer is the leading cause of cancer death in both men and women worldwide, accounting for 1.8 million new cases and 1.6 million deaths annually [1, 2]. Most lung cancers are detected at advanced stages, reducing the likelihood of cure. The 5-year survival rate, ranging from 50% for stage IA to 2% for stage IV, improves significantly when diagnosed at an early stage [3]. Thus, long-term survival in lung cancer depends mainly on early detection and immediate start of treatment [4]. However, there are as yet no effective early detection tools for lung cancer, so patients cannot receive timely treatment, leading to unfavorable clinical outcomes.

Traditional pathological biopsy improves the accuracy of diagnosis, but such invasive procedures can cause the patient substantial inconvenience and pain. The current strategy for lung cancer screening is low-dose computed tomography (LDCT) in high-risk populations. Meta-analysis [5, 6] demonstrated that LDCT is more sensitive in discovering stage I lung cancers and all cancers than chest X-ray or no screening, and has resulted in a 20% reduction in lung cancer mortality [7]. However, LDCT was apt to possess higher false-positive rates as what the meta-analysis showed, limiting its widespread application as a screening tool [8]. Molecular markers may help identify high-risk populations of lung cancer that may benefit from lung cancer LDCT screening, thereby reducing unnecessary follow-up LDCT scans and radiation exposure. In addition, combination of molecular markers and LDCT screening for diagnosing lung cancer may reduce excessive false positive results [9]. Thus, identifying more reliable and accurate serum tumor markers for lung cancer remains a high priority.

A handful of molecular biomarkers have been applied to clinical testing, such as carcinoembryonic antigen (CEA), neuron-specific enolization enzyme (NSE), cytokeratin 19 fragment (CYFRA21-1), carbohydrate antigen (CA) 125, and CA199. However, these molecules are rarely used as early biomarkers because of their low sensitivity and specificity, and because false-positive results can occur as a result of infection, benign tumors, pregnancy, and other factors [10].

Lung cancers can trigger host immune responses and elicit antibodies against tumor antigens [11]. This response occurs because these tumor-associated antigens (TAAs) are altered to some degree. They may be mutated (e.g. p53) [12], misfolded [13], overexpressed (e.g. NY-ESO-1) [14], aberrantly degraded [15] or aberrantly glycosylated (e.g. MUC-1) [16]. Compared with the traditional lung cancer serological markers, antibodies against TAAs, called tumor-associated autoantibodies (TAAbs), have unique advantages. First of all, TAAbs have been detected not only at initial diagnosis of lung cancer [17], but also, in some cases, up to 5 years before cancer is diagnosed [18, 19], whereas TAAbs are absent or present at low levels in serum of healthy people and in patients with benign pulmonary tumors. Secondly, TAAbs have long half-lives in serum. Thirdly, especially in the early stage of tumor development, TAAb levels in serum are much higher than levels of TAAs [20].

The aim of this meta-analysis was to summarize the available evidence on the overall accuracy of TAAbs for the diagnosis of lung cancer.

Materials and Methods

Search strategy and study selection

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [21]. Two investigators (QJY and ZN) independently searched PubMed, Scopus, Web of Knowledge, Chinese National Knowledge Infrastructure (CNKI), Wanfang and Weipu databases without time limitations. The last search was conducted on 23 March 2018. The following retrieval strategy was used: "autoantibody or autoantibodies" and "lung cancer or lung carcinoma or lung neoplasm or pulmonary cancer or cancer of lung" and "sensitivity or specificity or accuracy". In addition, the reference lists of eligible articles were manually searched by the two investigators independently in order to obtain additional studies.

Two authors (QJY and ZN) independently assessed each study for eligibility. Discrepancies were resolved by consultation with a third author (SYC). Studies were included in the review if they fulfilled all the following criteria: (1) the work was an original research article published in English or Chinese; (2) human samples were analyzed; (3) the study examined TAAbs for diagnosing lung cancer and contained a control group; and (4) sufficient data were reported to calculate true positive (TP), false positive (FP), false negative (FN), and true negative (TN) rates for TAAbs. Case reports or case series involving fewer than 10 patients, conference proceedings, reviews, letters to the editor, and case reports were excluded because of the limited data reported.

Quality assessment and data extraction

The quality of the included studies was scored independently by two authors (QJY and ZN) according to the criteria of the Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) [22]. Four key domains were assessed (patient selection, index test, reference standard, flow and timing), and each domain contained seven "yes/no/unclear" questions. The following data were retrieved from each study: authors, country, tumor type, specimen type, gold standard, assay methods, and 2-by-2 tables showing rates of TP, TN, FP and FN. Detailed information about controls was also extracted. Controls in the included studies were either healthy or they had benign pulmonary diseases.

Data synthesis and analysis

Data were completed in Excel, then transferred to STATA 14.0 (Stata, College Station, TX, USA) and Review Manager 5.2 (The Cochrane Collaboration, Copenhagen, Denmark) for statistical analysis. For each study, pooled sensitivity and specificity and their 95% confidence intervals (CIs) were calculated using the bivariate random-effects model [23]. To provide potentially more clinically relevant outcomes, we also calculated for each TAAb a likelihood ratio, diagnostic odds ratio (DOR), and area under the curve (AUC).

Two authors (QJY and ZN) assessed studies for possible overlap in the populations analyzed. Data were pooled from overlapping populations as long as the different studies reported on different TAAbs or TAAb combinations. Otherwise, if studies with overlapping populations reported on the same TAAbs or TAAb combination, only the data from the largest study were used.

Heterogeneity induced by the nonthreshold effect was assessed using the Cochran Q method and the test of inconsistency (I^2). If $P < 0.05$ or $I^2 > 50\%$, heterogeneity exists [24]. Furthermore, subgroup and regression analyses were performed to explore potential sources of heterogeneity. Deeks' test was used to detect publication bias. All P values were calculated using a 2-tailed test, and $P < 0.05$ was regarded as statistically significant.

Results

Basic information about the included studies

A total of 468 articles were initially identified, of which 327 were excluded as duplicates, reviews, news reports, meeting records or other publication types that did not focus on lung cancer (Fig. 1). In the end, 53 articles were included, which examined the diagnostic efficacy of TAAbs against p53, c-myc, Survivin, NY-ESO-1, Cyclin B1, CAGE, GBU 4-5, p16, HuD and SOX2 [17, 25-76]. Other TAAbs were excluded from the review because relevant data were available from fewer than 3 articles [77-108]. Five of the included studies examined only small-cell lung cancer (SCLC)[45, 50, 52, 58, 67], and eight included only non-small cell lung cancer (NSCLC)[28, 47, 54, 55, 57, 59, 64, 109]. A total of 50 articles were based on serum specimens, while the remaining 3 were based on plasma samples. In 41 articles, diagnosis of lung cancer was based on histopathology or cytology; 12 articles did not report the standards used to diagnose lung cancer. A total of 50 articles measured TAAb levels using enzyme-linked immunosorbent assays (ELISAs), and the remaining 3 articles using immunoblotting (Supplementary Table 1 - for all supplemental material see www.karger.com/10.1159/000495935/). Mean absorbance or level of TAAbs in the control group plus 2-3 standard deviations (SDs) were used to identify positive samples.

Study quality

QUADAS-2 assessment of included studies showed that most studies had low risk of bias (Fig. 2 and Fig. 3) and that the studies were suitable for quantitative synthesis.

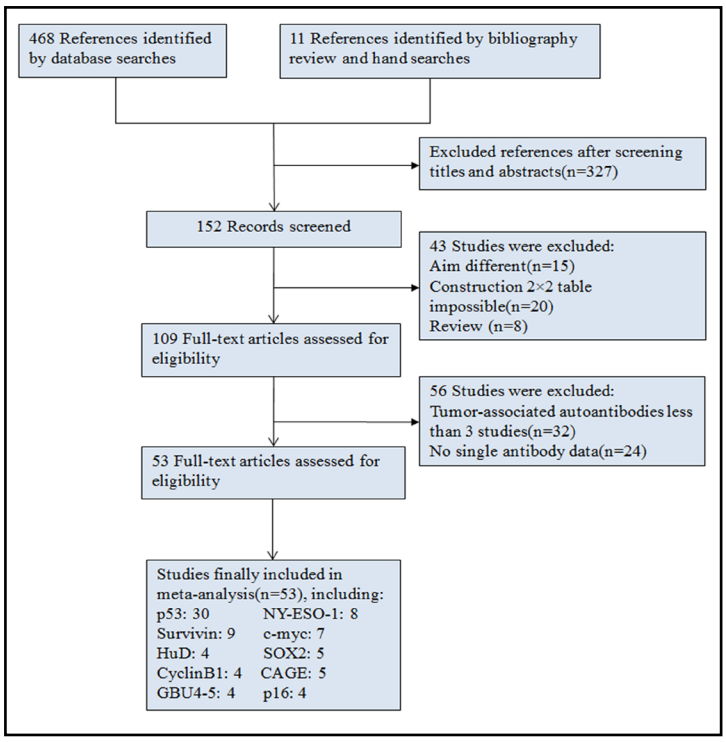

Fig. 1. Flow diagram of study selection.

Diagnostic performance of single TAAbs

Data were meta-analyzed using a bivariate model (Table 1). The meta-analysis showed that overall sensitivity of all TAAbs was low: TAAb against p53, 0.19 (95%CI 0.15–0.23); NY-ESO-1, 0.17 (95%CI 0.10–0.26); Survivin, 0.19 (95%CI 0.12–0.29); c-myc, 0.14 (95%CI 0.11–0.18); HuD, 0.17 (95%CI 0.12–0.24); SOX2, 0.14 (95%CI 0.06–0.30); Cyclin B1, 0.18 (95%CI 0.14–0.24); CAGE, 0.14 (95%CI 0.09–0.21); GBU 4-5, 0.07 (95%CI 0.02–0.22); and p16, 0.08 (95%CI 0.03–0.22). In contrast, the TAAbs showed excellent pooled specificity: p53, 0.98 (95%CI 0.97–0.98); NY-ESO-1, 0.98 (95%CI 0.96–0.99); Survivin, 0.99 (95%CI 0.97–0.99); c-myc, 0.98 (95%CI 0.96–0.99); HuD, 0.99 (95%CI 0.98–1.00); SOX2, 0.99 (95%CI 0.97–0.99); Cyclin B1, 0.98 (95%CI 0.96–0.99); CAGE, 0.98 (95%CI 0.96–0.99); GBU 4-5, 0.98 (95%CI 0.94–0.99); and p16, 0.97 (95%CI 0.94–0.99). AUCs were as follows: p53, 0.82 (95%CI 0.79-0.85); NY-ESO-1, 0.90 (95%CI 0.87-0.92); Survivin, 0.96 (95%CI 0.93-0.97); c-myc, 0.45 (95%CI 0.41-0.49); HuD, 0.82 (95%CI 0.79-0.85); SOX2, 0.93 (95%CI 0.90-0.95); Cyclin B1, 0.91 (95%CI 0.88-0.93); CAGE, 0.90 (95%CI 0.87-0.92); GBU 4-5, 0.91 (95%CI 0.88-0.93); and p16, 0.91 (95%CI 0.88-0.93). The SROC curve was generated for the four TAAbs reported by the largest number of studies (Survivin, p53, NY-ESO-1, c-myc), allowing overall assessment of diagnostic performance (Fig. 4).

Diagnostic performance of p53 TAAb for early stage I/II lung cancer

We also focused on the diagnostic value of TAAb for early stage lung cancer. Six studies on p53 TAAb [29, 30, 37, 39, 40, 51] were included for the meta-analysis, which reported the positive rate for this TAAb in different stages of lung cancer. The pooled sensitivity and specificity of p53 TAAb for early stage I/II lung cancer was 0.13 (95%CI 0.04-0.33) and 0.98 (95%CI 0.95-0.99), respectively. The AUC was 0.93 (95%CI 0.90-0.95), indicating a relatively high level of overall diagnostic accuracy of p53 TAAb for early stage lung cancer. Other TAAbs were not analyzed because fewer than three studies reported the positive rates of these TAAbs in different stages of lung cancer.

Subgroup analyses

Mutations in the p53 gene are present in up to 50% of NSCLC cases and 80% of SCLC cases [110]. Therefore we performed subgroup analysis to identify whether the presence of p53 TAAb could differentiate NSCLC (15 studies, 2, 478 patients) and SCLC (9 studies, 1, 630 patients). We also examined whether the same was true for NY-ESO-1 TAAb. The

Table 1. Summary estimates of diagnostic criteria and their 95% confidence intervals. TAAbs, tumor-associated autoantibodies; NSCLC, non-small cell lung cancer ; SCLC, small cell lung cancer ; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the curve

TAAbs	Cancer type	Sensitivity (95% CI)	Specificity (95% CI)	PLR(95% CI)	NLR(95% CI)	DOR(95% CI)	AUC	Deeks test P value
p53	Lung cancer	0.19 [0.15-0.23]	0.98 [0.97-0.98]	8.6 [5.9-12.4]	0.83 [0.79-0.87]	10 [7-15]	0.82 [0.79 - 0.85]	0.88
	NSCLC	0.20 [0.13-0.29]	0.97 [0.94-0.98]	6.5 [3.6-11.8]	0.82 [0.76-0.90]	8 [4-15]	0.79 [0.75 - 0.82]	0.05
	SCLC	0.27 [0.18-0.39]	0.97 [0.94-0.99]	9.9 [5.6-17.6]	0.75 [0.65-0.86]	13 [7-24]	0.79 [0.76 - 0.83]	0.10
NY-ESO-1	Lung cancer	0.17 [0.10-0.26]	0.98 [0.96-0.99]	7.0 [4.6-10.8]	0.85 [0.78-0.93]	8 [5-13]	0.90 [0.87 - 0.92]	0.07
	NSCLC	0.25 [0.14-0.40]	0.95 [0.86-0.98]	4.9 [2.6-9.1]	0.79 [0.70-0.90]	6 [3-11]	0.67 [0.63 - 0.71]	0.41
	SCLC	0.10 [0.06-0.18]	0.98 [0.96-0.99]	5.2 [2.1-13.0]	0.91 [0.85-0.98]	6 [2-15]	0.96 [0.94 - 0.97]	0.21
Survivin	Lung cancer	0.19 [0.12-0.29]	0.99 [0.97-0.99]	14.5 [4.6-45.8]	0.82 [0.74-0.92]	18 [5-60]	0.96 [0.93 - 0.97]	0.04
c-myc	Lung cancer	0.14 [0.11-0.18]	0.98 [0.96-0.99]	8.4 [3.9-17.9]	0.87 [0.84-0.91]	10 [4-21]	0.45 [0.41 - 0.49]	0.92
Cyclin B1	Lung cancer	0.18 [0.14-0.24]	0.98 [0.96-0.99]	8.1 [4.3-15.4]	0.83 [0.79-0.89]	10 [5-19]	0.91 [0.88 - 0.93]	0.99
CAGE	Lung cancer	0.14 [0.09-0.21]	0.98 [0.96-0.99]	6.2 [3.5-11.0]	0.88 [0.82-0.94]	7 [4-13]	0.90 [0.87 - 0.92]	0.91
GBU 4-5	Lung cancer	0.07 [0.02-0.22]	0.98 [0.94-0.99]	3.7 [0.5-26.7]	0.95 [0.85-1.05]	4 [0-31]	0.91 [0.88 - 0.93]	0.08
p16	Lung cancer	0.08 [0.03-0.22]	0.97 [0.94-0.99]	3.1 [1.1-8.8]	0.95 [0.87-1.03]	3 [1-10]	0.91 [0.88 - 0.93]	0.41
SOX2	SCLC	0.14 [0.06-0.30]	0.99 [0.97-0.99]	10.7 [5.7-20.0]	0.88 [0.77-0.99]	12 [6-24]	0.93 [0.90 - 0.95]	0.57
HuD	SCLC	0.17 [0.12-0.24]	0.99 [0.98-1.00]	21.3 [5.9-76.8]	0.84 [0.77-0.90]	25 [7-96]	0.82 [0.79 - 0.85]	0.24

results suggest that both TAAbs show greater diagnostic efficiency for SCLC than for NSCLC, albeit with low diagnostic efficacy (Table 1).

We also compared the diagnostic performance of p53 TAAb depending on whether the reference (control) group was healthy individuals or patients with chronic pulmonary disease. The p53 TAAb showed the following diagnostic parameters against healthy controls: sensitivity, 0.18 (95%CI 0.13-0.24); specificity, 0.98 (95%CI 0.97-0.98); PLR, 7.7 (95%CI 5.8-10.3); NLR, 0.84 (95%CI 0.79-0.89); DOR, 9 (95%CI 7-13); and AUC, 0.92 (95%CI 0.89-0.94). In contrast, the parameters against patients with chronic pulmonary disease were as follows: sensitivity, 0.16 (95%CI 0.12-0.21); specificity, 0.97 (95%CI 0.93-0.98); PLR, 4.9 (95%CI 2.4-9.8); NLR, 0.87 (95%CI 0.82-0.91); DOR, 6 (95%CI 3-12); and AUC, 0.54 (95%CI 0.5-0.58). These results suggest that, at least in the case of the p53 TAAb, using healthy individuals as controls provides higher diagnostic efficiency than using patients with chronic pulmonary disease.

Meta-regression analyses

Significant heterogeneity existed among studies of the p53 TAAb: I^2 values were 91.63% for sensitivity, 69.11% for specificity (Fig. 5), 13.88% for PLR, 85.48% for NLR and 100% for DOR (all $P < 0.05$). Therefore we conducted meta-regression analysis for data on this TAAb in which the odds ratio (OR) was used for binary classification of data, and log OR was used as the response variable. The covariates were the patient's geographic region, type of sample and assay method. The residual I^2 (I^2-res) value was 29.74%, suggesting that 29.74% of the residual variation could be explained by the heterogeneity, while the remaining 70.26% was explained among the studies. The adjusted R-squared was 41.92% in the covariate model, which may explain the variation among the studies. This variation may relate to the patient's geographic region ($P = 0.034$; Table 2), but it was not related to type of sample or assay method. Thus we conducted subgroup analysis of p53 TAAb performance based on the patient's geographic region (Table 3). Conclusive cut-off values could not be identified in this regression because of inaccurate data and the lack of a uniform standard. Meta-regression analysis was not performed for other TAAbs because of the limited number of studies.

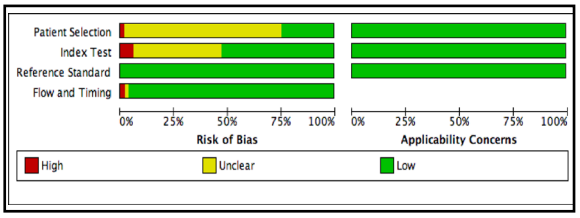

Fig. 2. Methodological quality graph.

Diagnostic performance of TAAb combinations

The included studies reported sufficient data to examine the diagnostic performance of two combinations of TAAbs. One combination was TAAbs against p53, NY-ESO1, CAGE, GBU4-5, Annexin 1 and SOX2 [48, 53, 111-113], which showed estimated sensitivity of 0.38 (95% CI 0.35–0.40) and specificity of 0.89 (95% CI 0.86–0.91). The other combination was TAAbs against p53, CAGE, NY- ESO-1, GBU4-5, SOX2, MAGE A4 and HuD [2, 53, 111, 114], which showed estimated sensitivity of 0.47 (95% CI 0.34–0.60) and specificity of 0.90 (95% CI 0.89–0.92).

Sensitivity analysis

Sensitivity analysis for p53 TAAb was performed to make sure that our findings were not overly influenced by any single study (Fig. 6). Comparison of pooled diagnostic parameters using all studies or all studies except for three outliers [33, 36, 37] showed that excluding the three studies reduced sensitivity from 0.19 to 0.17, DOR from 10 to 9 and PLR from 8.6 to 7.9, whereas it increased NLR from 0.83 to 0.85 and AUC from 0.82 to 0.91. Specificity in both cases was 0.98. Excluding the three studies reduced the I^2 for heterogeneity in sensitivity from 91.63% to 89.47% and in specificity from 69.11% to 31.03%. These results suggest that our meta-analysis with the full set of studies is reliable.

Publication bias evaluation

Except for studies of p53 TAAb and Survivin TAAb for diagnosing NSCLC and lung cancer, respectively, Deeks' funnel plots showed no evidence of publication bias for the TAAbs (all P > 0.05; Table 1).

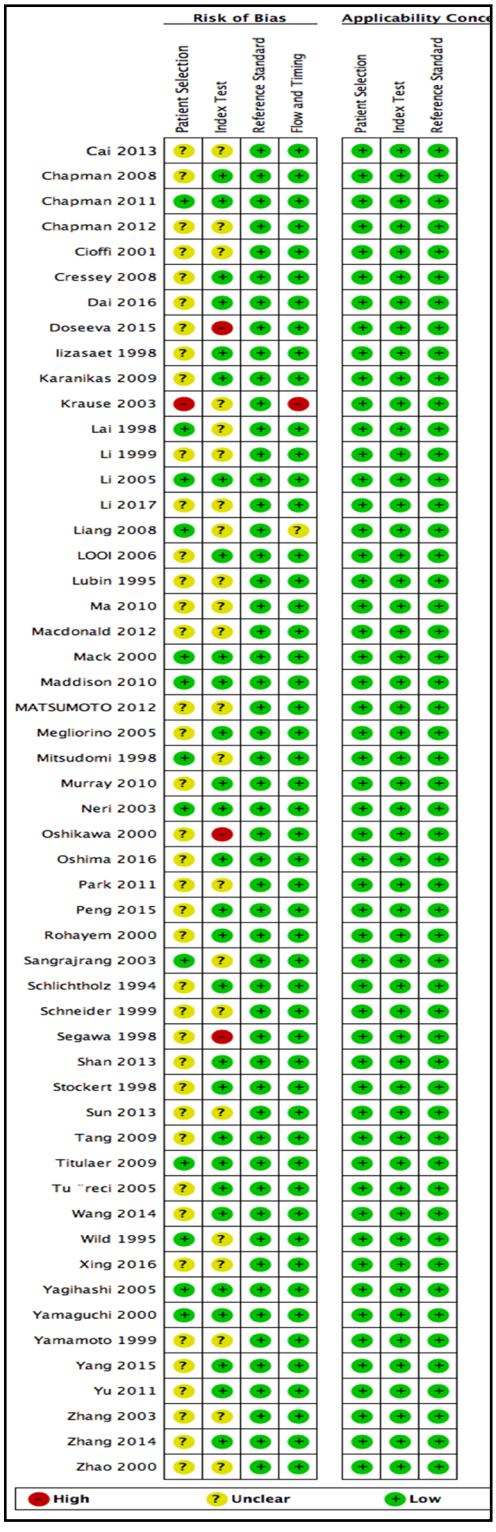

Fig. 3. Methodological quality summary.

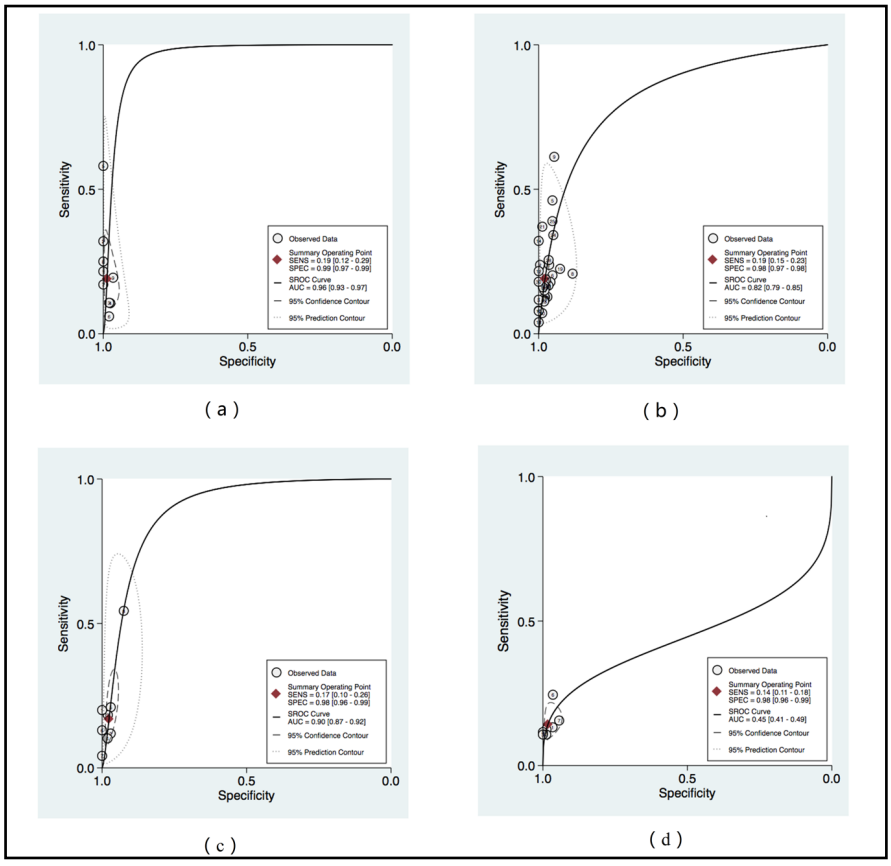

Fig. 4. Summary receiver operating characteristic (SROC) curve of autoantibodies for the diagnosis of lung cancer. a) Anti-Survivin autoantibody, b) anti-p53 autoantibody, c) anti-NY-ESO-1 autoantibody, d) anti-c-myc autoantibody. The number in each circle corresponds to the number of studies.

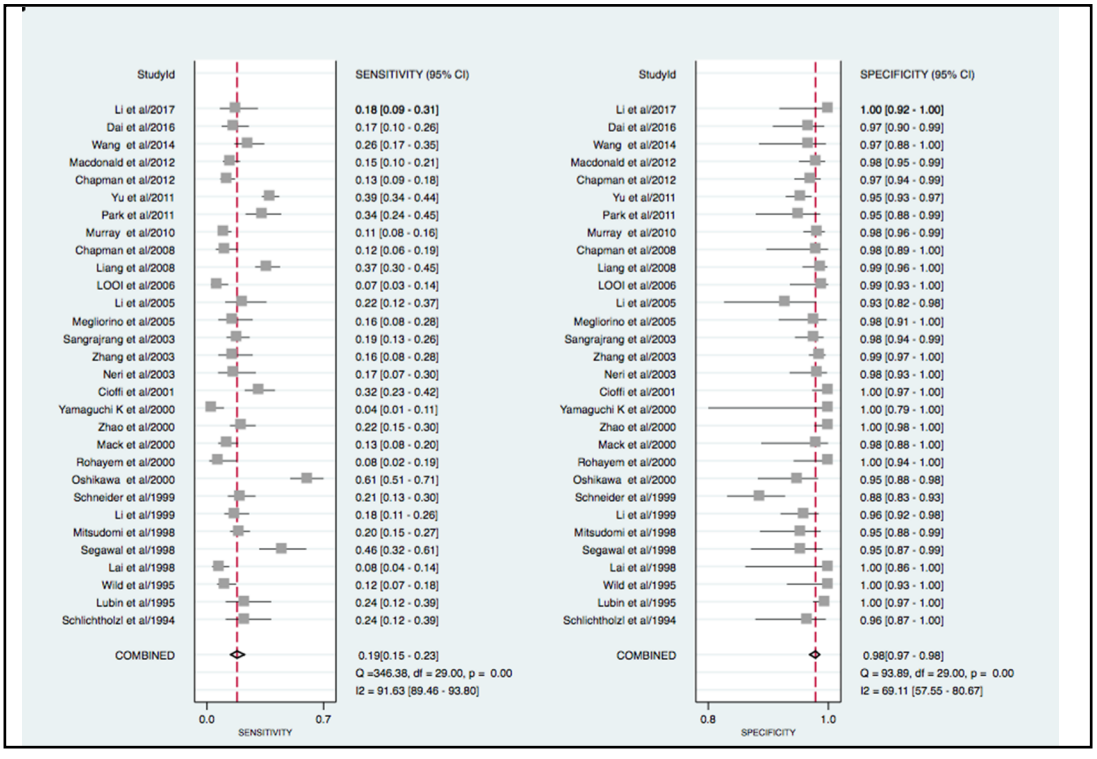

Fig. 5. Forest plot of diagnostic accuracy index of p53 TAAb in lung cancer. Sensitivity and specificity of p53 TAAb in diagnosis of lung cancer. The point estimates the sensitivity and specificity among the studies as solid squares. Error bars with 95% confidence intervals (CIs).

Table 2. Using the odds ratio (OR) for the meta-regression analysis in the binary classification of variable data. LogOR was used as response variables as well as ethnicity, specimen and method were as covariates Estimate of between-study variance tau2 =0.1712. Residual variation due to heterogeneity: I-squared_res = 29.74%. Proportion of between-study variance explained: Adj R-squared =41.92%. Joint test for all covariates with Knapp-Hartung modication: Prob > F = 0.1387

LogOR	exp（b）	Std.Err	t	P>|t|	[95%Conf.	Interval]
Patient's geographic region	.5033167	.1545677	-2.24	0.034	. 2677276	.9462143
Type of sample	1.157628	. 6786082	0.25	0.805	.3469447	3.862583
Assay method	2.782821	4.275418	0.67	0.511	.1182953	65.46406
_cons	3.847993	6.275298	0.83	0.416	. 1347142	109.9146

Table 3. Subgroup analysis of geographic region for p53 autoantibody. PLR, positive likelihood ratio; NLR, negative likelihood ratio;DOR, diagnostic odds ratio

Geographic region	Number of studies	I^2 for sensitivity	I^2 for specificity	I^2 for PLR	I^2 for NLR	I^2 for DOR
Total	30	91.63	69.11	13.88	85.48	100
Asia	14	92.88	36.01	0	89.40	90.37
Non-Asia	16	69.59	79.06	13.29	53.33	99.99

Discussion

The mortality of lung cancer is due primarily to late detection; early diagnosis is crucial for asymptomatic patients. TAAbs can be detected in many cancer patients prior to symptom onset [17, 48], raising the possibility that they may facilitate early diagnosis. Indeed, healthy people usually lack these TAAbs, even those at higher risk of lung cancer. These promising characteristics have led many researchers to explore the diagnostic potential of assaying TAAbs in peripheral blood as serological markers of lung cancer.

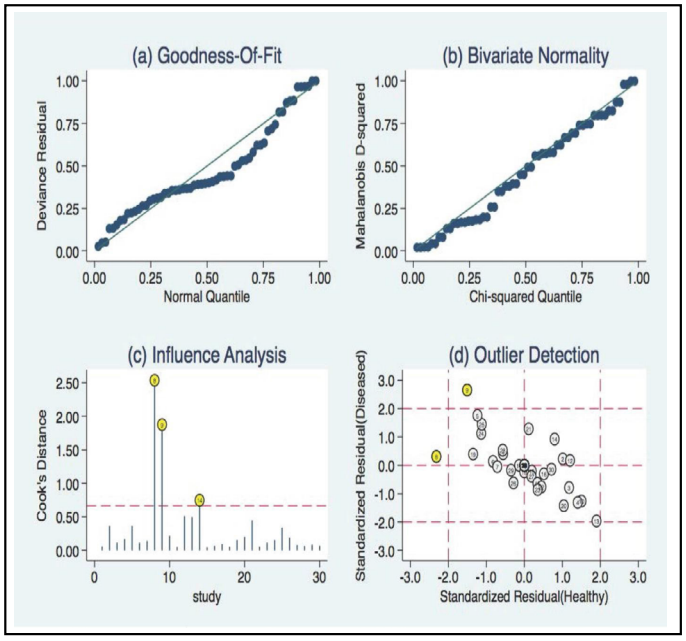

Fig. 6. Sensitivity analysis of anti-p53 autoantibody. a) Graphical depiction of residual-based goodness of fit, b) bivariate normality, c) influence analysis, d) outlier detection.

One recent review [109] indicated different single or combinations of multiple TAAbs have different diagnostic abilities for detecting patients at all stages of lung cancer, while the review did not report sensitivity, specificity and AUC for each TAAb. In our systematic review, each TAAb was analyzed using bivariate mixed-effect models, and larger numbers of references were included. Our systematic review of the available evidence suggests that TAAbs against p53, NY-ESO-1, Survivin, c-myc, HuD, SOX2, Cyclin B1, CAGE, GBU 4-5 and p16 show high specificity for diagnosing lung cancer but insufficient sensitivity. For example, PLRs were >10 (indicating >10-fold difference between pre- and post-test) only for TAAbs against Survivin, HuD, or SOX2 (Table 1). This means that a positive result for any of these TAAbs indicates a relatively high probability of lung cancer, which is consistent with the high specificities reported for these TAAbs. However, the NLRs

for these TAAbs were not low, indicating an inability to exclude the possibility of lung cancer.

SCLC progresses rapidly and disseminates widely, giving rise to low 5-year survival [115]. Most cases of SCLC (60-70%) are diagnosed at the extensive stage, reducing the possibilities for good prognosis [116-118]. This highlights the urgent need to develop serum biomarkers that might allow diagnosis of SCLC. Our meta-analysis suggests that p53 and NY-ESO-1 TAAbs show better diagnostic performance for SCLC than for NSCLC. A previous study suggested that the Hu TAAb may be useful in early diagnosis of SCLC [119]. Therefore future studies should investigate whether combining TAAbs against Hu, p53 and NY-ESO-1 can facilitate SCLC diagnosis.

The EarlyCDT®-Lung Test is a novel TAAb diagnostic test for the early detection of lung cancer allowing stratification of individuals according to their risk of developing lung cancer, which could permit a targeted approach to LDCT scanning for early lung cancer detection. The EarlyCDT®-Lung Test measures seven TAAbs against p53, NY-ESO-1, CAGE, GBU4-5, HuD, MAGE A4 and SOX2, which identify 47% of lung cancers with a high specificity of 90%[2, 53, 111, 114]. Moreover, the TAAbs detected in the test have not been shown to vary with age, gender or ethnicity [120], making the test more suitable for clinical screening. However, combinations of TAAbs may be associated with higher sensitivity but lower specificity than single TAAbs.

Survivin is an apoptosis-suppressing protein, promoting cell proliferation and inhibiting apoptosis [121, 122]. Once Survivin is overexpressed in lung cancer, it may lead to antibody responses to this protein. Antibodies to Survivin are one of the tumor-associated autoantibodies described most frequently in lung cancer [123, 124]. Our analysis shows that AUC and specificity of Survivin are relatively high. Future research should examine wehther Survivin should be included in the EarlyCDT®-Lung Test.

The present meta-analysis has some limitations. First, our exclusion of conference abstracts, letters to journal editors and unpublished data may have given rise to publication bias, such that our results overestimate actual diagnostic performance. Second, description of methodology was incomplete in some studies, leading to a QUADAS-2 assessment of "unclear". Third, a single TAAb was detected in a relatively small population of patients with lung cancer, which means that relying on TAAb individually may lead to a high FN rate. Fourth, most studies used ELISA to analyze serum TAAbs, while diagnostic cut-off values have not been established for lung cancer. Therefore, more researches are needed to confirm the optimized TAAb cut-off values. Fifth, all but one study [41] was retrospective, increasing the risk of bias in patient selection. Sixth, substantial heterogeneity was detected. In the case of studies of p53 TAAb, the heterogeneity reflected cancer type, source of control, and patient's geographic region as well as unidentified factors. Seventh, some studies did not report smoking status, especially in healthy controls, which leads to selection bias. For instance, the prevalence of p53-TAAbs was higher in smokers than in non-smokers [125, 126]. Moreover, smoking status was found to be the major contributor to levels of anti-Survivin TAAbs [127]. Future studies on TAAbs should consider smoking status. Our results highlight the need for more rigorous studies of TAAb combinations in the diagnosis of lung cancer.

Conclusion

TAAbs show low sensitivity and high specificity as serum diagnostic markers of lung cancer. Our results indicate that combinations or panels of autoantibodies may improve sensitivity but at the cost of specificity. Future research should focus on novel TAAb panels that may offer better diagnostic performance.

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Disclosure Statement

The authors declare no potential conflicts of interest.

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